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1 Gross, Elmer R., M.D.; Wright, Carroll S., M.D.; Oral Bismuth Therapy in Syphilis and Various Dermatoses—Paper presented at the Pennsylvania Medical Society Meeting, October 8, 1946 at Philadelphia, Pennsylvania.

2 Gross, Elmer R., M.D.; Howles, James K., M.D.; Non-Specific Treatment of Dermatoses and Adjunctive Therapy of Syphilis with Oral Sodium Bismuth Triglycollamate. Read before the Section of Dermatology and Syphilology Meeting of the Centennial Meeting of the A.M.A. at Atlantic City, New Jersey, June 12, 1947.

3 Year Book of Dermatology and Syphilology, 1946, page 31.

4 Sawicky, H. H., M.D.; Bistrimate (sodium bismuth triglycollamate) Administered by Mouth in the Treatment of Chronic Discoid Lupus Erythematosus. The Journal of Investigative Dermatology, vol. 9 #3 September 1947.

5 Howles, James K., M.D.; Treatment of Inflammatory-Dermatoses with Oral Bismuth (sodium bismuth triglycollamate). Southern Medical Journal, vol. 41 #11, pages 1033-1041, November 1948.

6 Pascher, Frances, M.D.; Sawicky, H. H., M.D.; Silverberg, M.G., M.D.; and Emmet, Richard, M.D.; Bistrimate for Lupus Erythematosus, Lichen Planus and other Dermatoses. Journal of Investigative Dermatology, vol. 10, #6, June 1948.

7 Miller, Thomas H., M.D. and Delaney, James R., M.D.; Oral Bismuth therapy in Dermatology. Archives of Dermatology and Syphilology, Vol. 60, August 1949.

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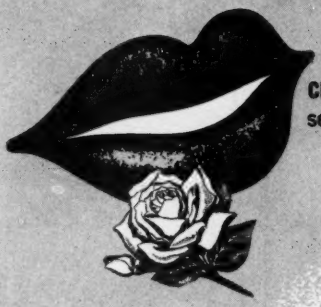

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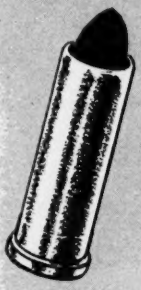

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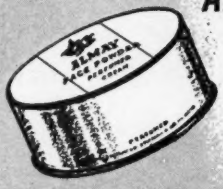

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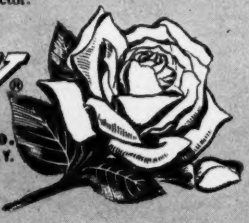

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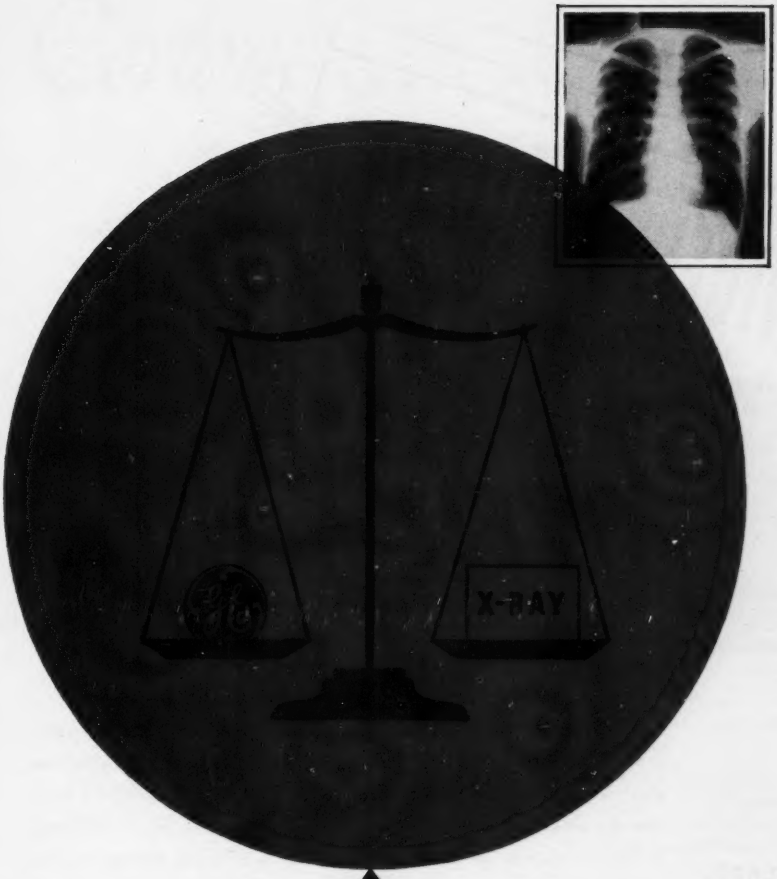

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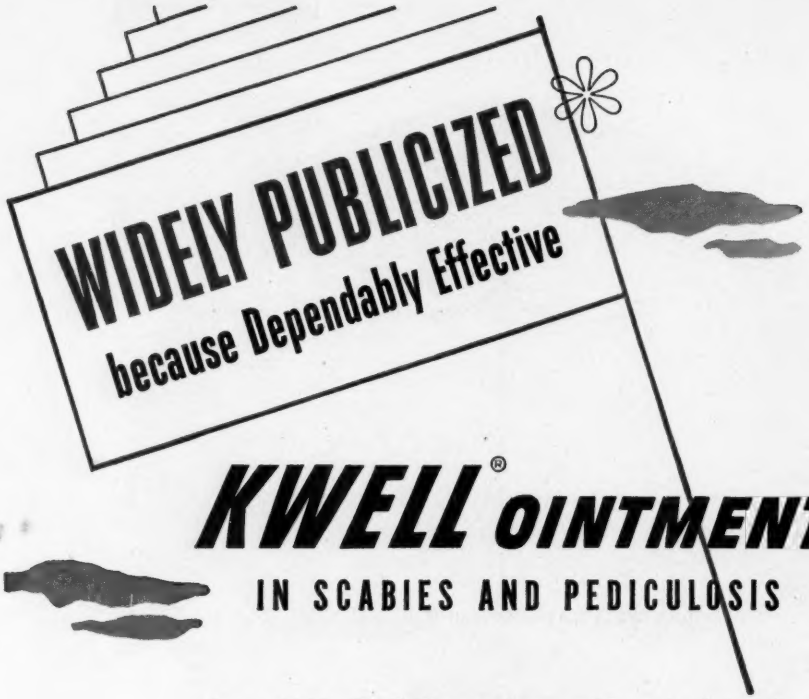

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5. Appel, B.: New England J. Med. 243:74 (July 20) 1950.

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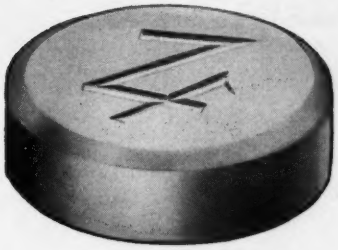

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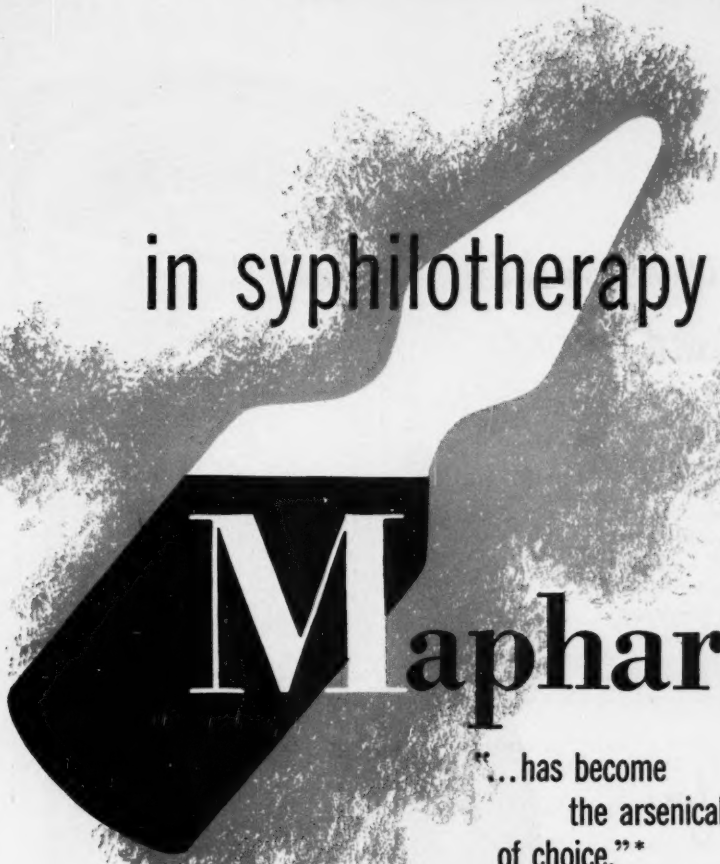

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2. Combes, F. C.: Coal Tar in Dermatology. Arch. Dermat. and Syph. **56**:583-588 (Nov.) 1947.
3. Ellis, C. C.: Wooldridge, W. E., and Weiss, R. S.: J. Invest. Dermat. **10**:6 (June) 1948.

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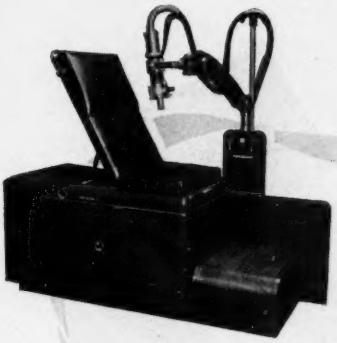

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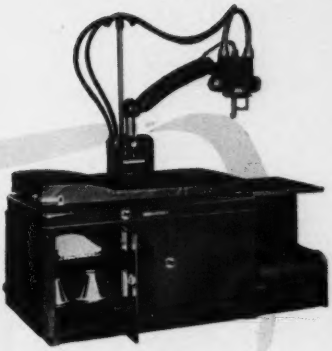

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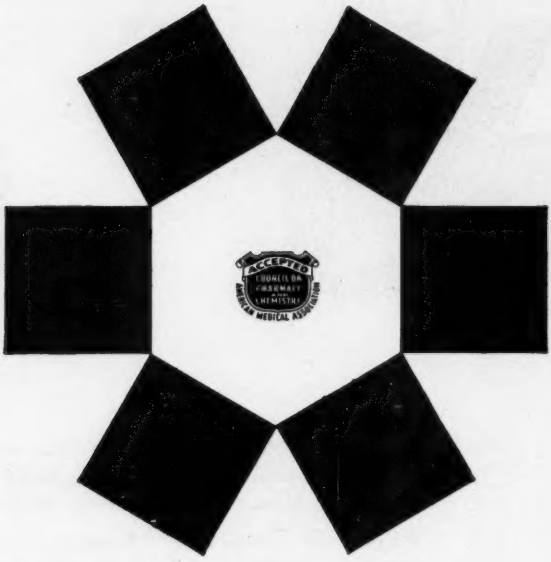

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ETIOLOGIC AND IMMUNOLOGIC CONCEPTS REGARDING SARCOIDOSIS

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CHICAGO

WHILE sarcoidosis has been receiving increasing attention in medical literature, there is still no agreement concerning its cause. It is the purpose of this paper to discuss some of the etiologic and immunologic concepts which have been advanced, in order to see what evidence there is for and against the various theories. By sarcoidosis is meant the systematized condition which goes under a variety of names, of which the three most prevalently used are Besnier-Boeck-Schaumann disease, lymphogranulomatosis benigna, and sarcoidosis. A local sarcoid reaction or sarcoid tubercle can arise as a result of a variety of stimuli and will not be further considered in this discussion except as a part of a systematized sarcoidosis.

The major theories concerning the causation of sarcoidosis are the following:

A. It is not an etiologic entity but can be caused by a variety of infectious agents, among them the tubercle bacillus, the spirochete of syphilis, the bacillus of leprosy, and others.

B. It is an etiologic entity. There are three main subdivisions of this theory: (1) It is a form of tuberculosis; (2) it is caused by a new and as yet unidentified organism, and (3) it is a systematized disease of the lymphoreticular (reticuloendothelial) tissue comparable to Hodgkin's disease and similarly of unknown origin, not necessarily on an infectious basis at all.

I shall start the discussion with the theory that the condition is of tuberculous causation, inasmuch as this view has had the most clinical and experimental study. Furthermore, to support this belief an immunologic concept has been advanced which would, if true, be of general and far-reaching importance.

POINTS IN FAVOR OF A TUBERCULOUS ORIGIN

The reasons advanced for believing that sarcoidosis has a tuberculous origin are (1) the development of frank tuberculosis in persons with sarcoidosis; (2) the occasional finding of tubercle bacilli in people with this disease, and (3) the relative anergy to tuberculin which a high percentage of persons with sarcoidosis display.

Significance of Development of Frank Tuberculosis.—How strongly does the development of a frank tuberculosis in patients with sarcoidosis argue for a tuber-

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culous causation? Such a finding could, of course, mean a conversion of a sarcoid form of tuberculosis into an ordinary form of tuberculosis if sarcoid were on a tuberculous basis, but this finding certainly does not necessarily indicate this. It could merely mean that sarcoidosis predisposes a person, especially the lungs and lymph nodes, toward the development of tuberculosis just as silicosis predisposes a person toward the development of pulmonary tuberculosis. It is interesting in this connection to note that, so far as can be gathered from the literature, a pulmonary tuberculosis does not supervene unless there was a pre-existing sarcoid of the lung. Hogan [1] suggested that a sarcoid lesion can impinge on a healed tuberculous lesion in such a way as to destroy the capsule that keeps the bacilli pent up and thus allow for the dissemination of tubercle bacilli in the lung itself, or through the blood stream to other parts of the body. Vivas and his associates [2] pointed out that a possible reason that tuberculosis is more frequent in persons with sarcoidosis than in the rest of the population may be that sarcoidosis is often mistakenly diagnosed as tuberculosis and the patient then placed in a tuberculous environment, where he is continuously exposed to virulent tubercle bacilli. Finally, Snapper [3] stated that a terminal development of tuberculosis in patients with Boeck's sarcoid can hardly be considered as proof of the tuberculous basis of the disease, since in patients with diabetes mellitus, Hodgkin's disease, and leprosy a terminal tuberculosis is not infrequent.

Interpretation of Bacteriologic Studies.—In attempting to evaluate the etiologic significance of the finding of tubercle bacilli in the tissues of people with sarcoidosis, it is necessary to consider the reliability of the evidence for their presence. This evidence must be scrutinized from two independent aspects, namely, (*a*) the validity of the bacteriologic findings, taking into account the technic of isolation as well as the interpretation of the findings, and (*b*) the accuracy of the diagnostic label "sarcoid."

The bacteriologic results will be reviewed according to the method used for the demonstration of the organisms. These are (*a*) the finding of acid-fast stained organisms in tissue from, or secretions of, sarcoid patients; (*b*) the development of tuberculosis in animals into which sarcoid tissue has been put, and (*c*) the growing of the organisms on culture mediums which have been inoculated with material from a sarcoid patient.

Concerning the finding of acid-fast organisms in the tissues as evidence for tuberculosis, it is a well-known fact that many varieties of bacteria and fungi other than tubercle bacilli have acid-fast characteristics. As an example of the caution needed before acid-fast organisms are labeled tubercle bacilli, Riley [4] related that in 40 patients repeated stains of sputum specimens and gastric aspirates were negative for acid-fast organisms except in four instances. In all four, concomitant

1. Hogan, G. F.: Sarcoidosis: A Report of 5 Cases with 1 Autopsy, Am. Rev. Tuberc. **54**:166, 1946.

2. Vivas, J. R.; Smith, H. A., and Jacobs, E. C.: Sarcoidosis: A Review of 20 Cases, Bull. U. S. Army M. Dept. **9**:829, 1949.

3. Snapper, I.: On Boeck's Sarcoidosis, Connecticut M. J. **12**:99, 1948.

4. Riley, E. A.: Boeck's Sarcoid: A Review Based upon a Clinical Study of 52 Cases, Am. Rev. Tuberc. **62**:231, 1950.

as well as subsequent smears and cultures were negative for tubercle bacilli. Thus it is believed that the positive findings in the four instances were laboratory errors or nonpathogenic acid-fast bacteria other than tubercle bacilli. Furthermore, when such organisms have been demonstrated they have usually been found in non-sarcoidal tissue of a sarcoid patient. Rubin and Pinner [5] stated, "In our case, tubercle bacilli were easily found in sections through caseated lesions but never in those through noncaseated foci." In other words, regardless of the nature of the acid-fast organisms, they would appear to be adventitial findings in cases of sarcoidosis.

When the inoculation experiments are reviewed, it is seen that it is rare for tuberculosis to develop in an inoculated animal. Should tuberculosis develop at all, it is nearly always only after several passages or after a protracted time. Lindau [6] commented regarding this as follows:

> Another source of error is that these guinea pigs are usually kept under observation for a long time up to one year and it is a well-known fact that guinea pigs living for more than three months in a room where tuberculous animals are kept may acquire a spontaneous tuberculosis.

Pinner,[7] in a detailed article written in 1938 on "noncaseating tuberculosis" (the term he preferred for sarcoidosis), commented regarding the then existing bacteriologic studies [8] as follows:

> Considering the great number of attempts to demonstrate tubercle bacilli in the specific lesions, the relatively few positive results are not impressive. Kissmeyer stated in 1932 that he had found in the literature 39 cases of Boeck's disease in which animal inoculation was done and that 7 of them had given what seemed to be positive results. Since then many more attempts have been reported, most of them with negative results.
>
> In Table 2 I have summarized all positive bacteriological findings that I was able to find in the literature. The number of positive results is very small; the number of completely convincing positive results is insignificant. Practically all positive animal inoculations are represented by extremely slowly progressive disease or by atypical findings, such as strictly localized lesions, or tuberculous manifestations occurring only after animal passage. For this reason, critics question the reliability of these findings and suggest the likelihood of spontaneous infection. All these arguments are inconclusive, since the original authors often omit the description that could identify an inoculation tuberculosis.

Adherents of tuberculous causation allege that the reason the organisms are found so rarely in the lesions is that by the time the diagnosis is clinically suspected (at which time the biopsy is usually done) sufficient time has elapsed for immune processes to come into being which either destroy the organisms or render them

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5. Rubin, E. H., and Pinner, M.: Sarcoidosis: 1 Case Report and Literature Review of Autopsied Cases, Am. Rev. Tuberc. **49**:146, 1944.

6. Lindau, A.: Are Benign Lymphogranuloma (Boeck's Sarcoid) and Uveoparotid Fever of Tuberculous Origin or Not? Acta path. et microbiol. scandinav., supp. 37, p. 357, 1938.

7. Pinner, M.: Noncaseating Tuberculosis: Analysis of the Literature, Am. Rev. Tuberc. **37**:690, 1938.

8. Pinner did not give the total number of attempts to demonstrate tubercle bacilli. Such a figure would be of interest in order to know out of how many efforts tubercle bacilli were found. The statement of Kissmeyer to which he refers is found in the following reference: Kissmeyer, A.: La maladie de Boeck: Sarcoides cutanees benignes multiples, Copenhagen, Levin & Munksgaard, 1932.

incapable of reproduction.[9] In support of this view Kyrle's [10] case is usually quoted. I should like to offer Pautrier's [11] remarks anent this case:

> Supporters of the tuberculous theory have made much of the case described by Kyrle, in which numerous tubercle bacilli were found scattered in a lymphocytic and histiocytic infiltration in a biopsy taken from sarcoid lesions only ten days old *(an early date for a diagnosis)* [italics mine]. On the thirty-sixth day, however, biopsy showed the bacilli to have disappeared, and at the same time the infiltration had taken on an epithelioid type. On the ninety-fourth day the infiltration had completely disappeared. Both the precocity of the clinical diagnosis and the unusual speed with which the lesions resolved are striking features of this case. On the other hand, out of two guinea-pigs inoculated with blood from the patient, one died with tuberculosis. The evidence points to the fact that this patient had tuberculosis and was in a period of bacillaemia.

According to Schaumann,[12] Kyrle's case was one of lupus vulgaris.

In Table 1, I have compiled the bacteriologic studies [13] that have been done (or reported) since Pinner. The table makes no claim to completeness and is almost certainly not complete. It merely lists the bacteriologic studies included in the articles that I have read. The table does not include any of the culture studies and/or animal inoculations with sputum or other secretory or excretory material.

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9. The validity of such a theory is discussed in detail later in this paper. At this point I should merely like to remark that it is not at all unusual for a person with concomitant sarcoidosis and tuberculosis to have demonstrable tubercle bacilli in the latter lesions and none in the former (Rubin and Pinner [5]). Another example is one given by Kveim: "In the case of a patient suffering from open pulmonary tuberculosis coincidental to his sarcoid of Boeck, all tests (with sarcoid material) were negative, whereas growth was of course obtained from the tuberculous sputum" (Kveim, A.: Some Remarks on the Aetiology of Boeck's Sarcoid, Acta dermat.-venereol. **28**:169, 1948). This would mean that the immune processes were at work in the extrapulmonary tissues but not in the pulmonary, a singular state of affairs.

10. Kyrle, J.: Die Anfangsstadien des Boeckschen Lupoids: Beitrag zur Frage der tuberculösen Ätiologie dieser Dermatose, Arch. Dermat. u. Syph. **131**:33, 1921.

11. Pautrier, L. M.: Sarcoidosis, Brit. J. Tuberc. **42**:1, 1948.

12. Schaumann, J., cited by Snapper.[3]

13. (*a*) Anglin, A.: Sarcoidosis, Canad. M. A. J. **56**:177, 1947. (*b*) Bjornstad, R. T.: Tuberculin Sensitivity in Boeck's Sarcoid, Acta tuberc. scandinav. **24**:15, 1950. (*c*) Carnes, W. H., and Raffel, S.: A Comparison of Sarcoidosis and Tuberculosis with Respect to Complement Fixation with Antigens Derived from the Tubercle Bacillus, Bull. Johns Hopkins Hosp. **85**:204, 1949. (*d*) Curtis, A. C., and Grekin, R. H.: Sarcoidosis: III. A Review, M. Clin. North America **33**:31, 1949. (*e*) Danbolt, N., and Brandt, A.: Sarkoidähnliche Hauttuberkulose, durch Hühnertuberkelbacillen hervorgerufen, Arch. Dermat. u. Syph. **178**:76, 1938-39. (*f*) Harrell, G. T.: Generalized Sarcoidosis of Boeck: Clinical Review of 11 Cases, with Studies of Blood and Etiological Factors, Arch. Int. Med. **65**:1003 (May) 1940. (*g*) Hogan.[1] (*h*) Kissmeyer, cited by Lindau.[6] (*i*) Kulwin, M. H.; Feldman, W. H.; Hinshaw, H. C., and Montgomery, H.: Sarcoidosis: A Clinical and Laboratory Study of 17 Cases, Minnesota Med. **32**:989, 1949. (*j*) Kveim, A.: Some Remarks on the Aetiology of Boeck's Sarcoid, Acta dermat.-venereol. **28**:169, 1948. (*k*) Longcope, W. T.: Sarcoidosis, or Besnier-Boeck-Schaumann Disease: Frank Billings Lecture, J. A. M. A. **117**:1321 (Oct. 18) 1941. (*l*) Nadler, W. H.: Sarcoidosis, J. Iowa M. Soc. **39**:367, 1949. (*m*) Rich, A. R.: The Pathogenesis of Tuberculosis, Springfield, Ill., Charles C Thomas, 1944, p. 722; (*o*) ibid., p. 455. (*p*) Ricker, W., and Clark, M.: Sarcoidosis: Clinico-Pathologic Review of 300 Cases, Including 22 Autopsies, Am. J. Clin. Path. **19**:725, 1949. (*q*) Riley.[4] (*r*) Rosenthal, J., and Feigin, I.: Boeck's Disease (Boeck's Sarcoid), Arch. Path. **45**:681 (June) 1948. (*s*) Snapper, I., and Pompen, A. W. M.: Pseudo-Tuberculosis in Man: Part I. Besnier-Boeck's Disease: Visceral Localisation of the Sarcoids of Boeck, Haarlem, Netherlands, de Erven F. Bohn 1938. (*t*) Stuart, B. M.: Sarcoidosis of Boeck: Metabolic Studies of 3 Cases, Am. J. M. Sc. **208**:717, 1944. (*u*) Thomas, C. C.: Sarcoidosis, Arch. Dermat. & Syph. **47**:58 (Jan.) 1943. (*v*) Lindau.[6]

TABLE 1.—*Culture or Animal Inoculation Studies with Sarcoid Tissue Obtained on Biopsy or Autopsy*

Investigator	Number of Patients from Whom Tissue Was Taken*	Animal Inoculation Done	Species† Employed	Cultures Done‡	Results of Animal Inoculation or Culture
Anglin [12a]	2	Yes	Guinea pig, fowl	Not stated	Negative
Bjornstad [12b]	71	Yes	Not stated	Yes	Negative
Carnes and Raffel [12c]	16	Yes	Guinea pig	Not stated	Negative
Curtis and Grekin [12d]	19 §	Yes	Guinea pig	Not stated	Negative
Danbolt and Brandt [12e]	6	Yes	Guinea pig, fowl, rabbit	Not stated	Negative
Harrell [12f]	5	Yes	Guinea pig, rabbit, fowl, rat, mouse	Yes, a variety of mediums	Negative ‖
Hogan [1]	1	Yes	Guinea pig	Yes	Negative
Kissmeyer [12h]	15	No	.....	Yes ¶	Negative
Kulwin [12i]	16	Yes	Guinea pig, fowl, rabbit	Yes, a variety of mediums	Negative
Kveim [12j]	33	Yes	Guinea pig, fowl, rabbit; 172 animals used	Yes, a variety of mediums	Negative ‡
Lindau [6]	10	Yes	Not stated	Yes	Negative **
Longcope [12k]	At least 8	Yes	Guinea pig, rabbit, pigeon	Yes	Negative ††
Nadler [12l]	2	Yes	Guinea pig	Not stated	Negative
Pautrier [11]	Not stated	Yes	Guinea pig, rabbit	Not stated	Negative ‡‡
Rich [12n]	Not stated	Yes	Guinea pig, rabbit, fowl	Not stated	Negative
Ricker and Clark [12p]	36	Yes	Guinea pig	Yes	2 positive §§
Riley [4]	8	Yes	Guinea pig	Not stated	Negative ‖‖
Rosenthal and Feigin [12r]	1	Yes	Guinea pig	Not stated	Negative
Snapper [12s]	8	Yes	Guinea pig	Not stated	Negative
Stuart [12t]	2	Yes	Guinea pig	Not stated	Negative ¶¶
Thomas [12u]	6	Yes	Guinea pig	Yes	Negative
Total	At least 265	....	.....	.....	2 positive §§

* In many cases the tissue from one patient was put into more than one animal or inoculated into more than one culture tube. The chart gives only the number of patients from whom the tissue was taken.

† Where more than one species of animal was inoculated, tissue from each of the individual patients was not necessarily put into each of the species employed.

‡ When a variety of mediums were utilized it does not mean that each tissue was placed on all the mediums.

§ The article is ambiguous as to just how many animals were inoculated and just what tissue was used as the inoculum.

‖ In two cases the cultures were positive, but not for tubercle bacilli.

¶ The information is taken from Lindau's article, and he is not explicit as to the nature of the material implanted on the culture mediums.

‡ Kveim stated that tuberculosis developed in one animal about two years after the inoculation. He regarded this as an accidental stable infection.

** Lindau stated, "Since then I have inoculated animals and made cultures with material from about ten cases, all of them active and without fibrous healing. All the tests were negative, and Dr. K. A. Jensen, the well-known expert at the Danish State Serum Institute, who kindly controlled my work by testing the same material simultaneously, obtained the same negative result."

†† Longcope concluded that there is no evidence to support the view that sarcoidosis is caused by human, bovine, or avian tubercle bacilli.

‡‡ Pautrier commented, "I have never been able to obtain a positive inoculation from sarcoid tissue in any of the cases I have investigated personally. May I cite one case which allowed me to establish the identity of sarcoidosis and Heerfordt's syndrome? This was a most striking example of multiple recent fresh lesions, a confluent eruption of sarcoids over the whole body along with glandular enlargement and involvement of the lungs. One would have expected that if ever a positive result for the identification of the tubercle bacillus in sarcoidosis was to be obtained, this case should have been the ideal one. Twelve rabbits and guinea pigs were inoculated in various sites—skin, muscle, anterior chamber of the eye and brain—and, in addition, blood from the patient was inoculated into the testis. Prolonged observation of these animals over several months failed to show any evidence of tuberculosis, and the patient has recovered from his lesions spontaneously after several months."

In view of the fact that several authors have quoted Pautrier as having obtained positive inoculation results, I have checked these references.

Longcope and Pierson (*Bull. Johns Hopkins Hosp.* **60**: 223, 1937) referred to Pautrier as reporting a positive inoculation (*Bull. Soc. franç. dermat. et syph.* **41**: 1027, 1934). In this reference it will be found that Pautrier was talking about "miliary lupoids of the French authors," which he very clearly and unambiguously stated should be removed from the sarcoid group and put in with the true skin tuberculoderms. In his article in the French "Practice of Dermatology" (Darier and others: Nouvelle Pratique Dermatologique, Paris, Masson & Cie, 1936, Vol. 3, p. 630), he explicitly mentioned this case and put it in with the papulonecrotic tuberculides. Pinner [7] listed among the positive reports one by Pautrier and Glasser (*Bull. Soc. franç. dermat. et syph.* **43**: 505, 1936). In the original the authors referred to their result as a probable positive.

§§ Apparently 36 animals were inoculated and 26 cultures were done. The authors did not furnish information as to the source of the material for the inoculations or the cultures. One inoculation and one culture were positive. The article did not state whether these were from the same patient or not. Several of the authors' patients had a concomitant frank tuberculosis. It is not possible to tell whether the positive results were from these.

‖‖ Sputum, biopsy, and autopsy material were used.

¶¶ The source of material was not stated.

Such reports are very numerous and the results are almost entirely negative except with sputum specimens from patients in whom there was a concomitant frank pulmonary tuberculosis. In cases of pulmonary sarcoidosis, no matter how extensive the involvement, the sputa have not contained tubercle bacilli. In addition, no mention is made in the table of the equally numerous attempts to demonstrate acid-fast organisms by histologic means. Such attempts have also been almost 100% unsuccessful. A comment on some of this work was made earlier in this article.

Since Pinner's report in 1938, to my knowledge the only compilation of positive bacteriologic findings has been that of Schröpl.[14] Table 2 lists the cases[15] given by Schröpl, excluding those already listed by Pinner. This table appears after the section on Diagnostic Criteria for Sarcoidosis.

Diagnostic Criteria for Sarcoidosis: In assessing the reports of cases of sarcoid in which tubercle bacilli were found, it is necessary, as was mentioned earlier, to examine the accuracy of that diagnostic label and to see just what is meant by the terms "sarcoid" and "sarcoidosis."

As has already been stated, a differentiation must be made between a localized sarcoid reaction and the systematized disease sarcoidosis. A local sarcoid reaction can develop in response to a variety of stimuli, one of which is the tubercle bacillus. As an example let me quote from Freudenthal[16]:

> In addition, when examining serial sections of lupus nodules I found that, while the bulk of the nodule consisted of typical lupus tissue, sometimes one or two tubercles consisted of epithelioid cells only, with no or little infiltration around them, thus showing a sarcoid structure.
>
> Recently an untreated lupus nodule was sent to me that, to my surprise, on histological examination proved to consist almost entirely of sarcoid tissue.

Freudenthal went on to state that this nodule came from a case that was clinically typical of lupus, and the patient exhibited a strongly positive tuberculin reaction. But it should be clearly realized that local sarcoid reactions, whether evoked by the tubercle bacillus or not, do not constitute the entity "sarcoidosis." Klemperer,[17] in discussing collagen diseases, stated, " . . . . an apparent similarity in histologic picture does not denote identity of tissue lesions, and certainly not unity of process and pathogenesis." This comment would appear to be quite relevant to the present discussion.

In the present state of our knowledge it is, of course, impossible to state with certainty what criteria are necessary in order to make a diagnosis of sarcoidosis,

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14. Schröpl, E.: Zur Ätiologie und Pathogenese der Boeckschen Krankheit, Arch. f. Dermat. u. Syph. **183**:545, 1942.

15. (*a*) Danbolt and Brandt.[13e] (*b*) Ishikawa, M.: Ein Fall von Boeckschen Sarkoid, bei dem bovine Tuberkelbacillen kultiviert wurden, abstracted, Zentrabl. Haut- u. Geschlechtskr. **68**:19, 1942. (*c*) Leder, cited by Schröpl.[14] (*d*) Yamazaki, J.: Bakteriologische Untersuchungen über Hauttuberkulose, Jap. J. Dermat. & Urol. **43**:96, 1938. (*e*) Yamazaki, J., and Harada, G.: Zwei Fälle von Boeckschem Sarkoid mit positivem Tuberkelbazillenbefund im Herde, Jap. J. M. Sc., XIII, Derm. & Urol. **2**:177, 1941. (*f*) Yamazaki, J., and Horio, H.: Ein Fall von Lupoid Boeck mit positivem Tuberkelbazillenbefund, Jap. J. Dermat. & Urol. **47**:83, 1940.

16. Freudenthal, W.: Sarcoid, Brit. J. Tuberc. **42**:11, 1948.

17. Klemperer, P.: The Concept of Collagen Diseases, Am. J. Path. **26**:505, 1950.

but surely there must be evidence of systematization of the sarcoid process. Pinner,[18] a student for many years of this disease, had this to say in one of his last writings (1946) on the subject:

Some experiences which I have gathered since the publication of my literature review on sarcoidosis in 1938 have taught me the desirability of differentiating between sarcoid and sarcoidosis. The latter term should be reserved for the disease with its disseminated foci. The former term, used as an adjective, should describe the histologically characteristic structure. The significance of the differentiation is twofold: (1) As mentioned in my review, sarcoid structures have been produced in patients with sarcoidosis by the injection of nonspecific material. (2) I have seen in a few cases one single sarcoid tubercle as an accidental postmortem finding in patients who had neither tuberculosis nor sarcoidosis. One or two single but diagnostically unquestionable foci certainly do not justify the diagnosis of sarcoidosis which is a systemic disease. The pathologist who is confronted with a biopsy specimen containing a few

TABLE 2.—*Results of Culture and Animal Inoculation in the Cases Reported by Schröpl,* Excluding Those on Pinner's 1938 List*

Investigator	Number of Cases Reported	Bacteriologic Information Furnished by Schröpl
Danbolt and Brandt †	1	Inoculation of guinea pig negative but avian tuberculosis developed in a hen and rabbit
Ishikawa ‡	1	Culture from the tissue was positive; in a guinea pig inoculated with tissue swollen nodes in which there were many tubercle bacilli (bovine type) developed
Leder §	1	Excised material was inoculated into 2 guinea pigs; enlarged inguinal nodes from which tubercle bacilli were cultured developed in 1 of the 2 pigs
Schröpl ‖	2	In both cases positive cultures from the tissue were obtained; in 1 tubercle bacilli (human type) were found by animal inoculation as well
Yamazaki ¶	2	In 1 case tubercle bacilli (human type) were cultured from tissue; in the other they were demonstrated by passage through guinea pig
Yamazaki and Harada ♯	2	Authors merely stated that they demonstrated bacilli
Yamazaki and Horio **	1	Tubercle bacilli (bovine type) were cultured from involved tissue
Total	10	

* Schröpl also lists several other authors who allegedly found tubercle bacilli on either culture or animal inoculation in tissues other than the skin. Schröpl gives no information either clinical or bacteriologic, about these cases. They will not be discussed in this article.

† Danbolt and Brandt described a case identical with the nodular form of Boeck's sarcoid. Old tuberculin gave a weak reaction, but avian tuberculin produced a definite positive. It is difficult to understand why this case was included by Schröpl, as it was reported under the title of "Sarkoidähnliche Hauttuberkulose durch Hühnertuberkelbacillen hervorgerufen." In their conclusions the authors state, "Der Fall wird als eine sarkoidähnliche Hauttuberkulose und nicht als ein Boecks Sarkoid aufgefasst; indem diese Krankheit unserer Meinung nach kaum von Tb verursacht wird." [The case is regarded as a sarcoid-like skin tuberculosis and not as Boeck's sarcoid, since in our opinion this disease can scarcely be caused by tuberculosis.]

‡ In Ishikawa's case, according to the abstract in the *Zentralblatt*, there was a single lesion on the left cheek. No mention was made of any involvement elsewhere. The entire lesion was excised, and tubercle bacilli were demonstrated. The abstract gave no information as to how this was done.

§ Leder's case was not consulted in the original. There was not enough information given by Schröpl to allow me to discuss the case critically.

‖ In Schröpl's study, in one of the histologic sections of the second case there was definite necrosis, which, as he himself remarked, is unusual for Boeck's sarcoid and speaks for ordinary tuberculosis.

¶ Yamazaki's data were taken from his general article, "Bacteriologic Investigations in Skin Tuberculosis." Among the cases studied were two of "lupoid Boeck." The author gave no description of the patients other than the statement that both had typical "lupoid Boeck" on clinical and histologic grounds.

♯ In my opinion, both of Yamazaki and Harada's cases were instances of skin tuberculosis with a sarcoid-like reaction, for the following reasons: (*a*) In both cases there were previous lesions suggestive of active tuberculosis (Case 1, an exudative pleurisy; Case 2, tuberculous [?] glands of the neck); (*b*) in neither case was there evidence of a systematized sarcoidosis (negative pulmonary findings, negative bone findings), and (*c*) in both cases there was a relatively high sensitivity to tuberculin as shown by a positive Pirquet reaction.

** The case of Yamazaki and Horio was that of a female with lesions resembling Boeck's sarcoid of the face. On pressure the lesions yielded the appearance of a lupus. There were some lymph-node swellings. Roentgenograms of lung and bones were normal. There were typical histologic findings for sarcoid. Reaction to the Mantoux test was weakly positive. Tubercle bacilli were seen in sections of affected tissue. Some years previously the patient had had an exudative pleurisy. It would seem definite that this case, with the negative systemic findings and the appearance on pressure of a lupus, plus the positive tuberculin and positive bacillary findings, is one of lupus vulgaris with a sarcoid-like architecture.

18. Pinner, M.: On the Etiology of Sarcoidosis, Am. Rev. Tuberc. **54**:582, 1946.

characteristic sarcoid tubercles should probably report no more than "sarcoid tubercles"; he cannot know whether the patient has sarcoidosis. If such single lesions are included in the diagnosis sarcoidosis, the etiological problem becomes needlessly complicated. It is also pertinent to recall that the clinical and roentgenological diagnosis of sarcoidosis is beset with difficulties and uncertainties. The appearance of the chest roentgenogram is suggestive at best, but not pathognomonic. It is even conceivable that disseminated pulmonary lesions are not due to sarcoidosis in some patients in whom biopsies of lymph nodes contain sarcoid structures.

To sum up, the failure to distinguish between systemic sarcoidosis and a sarcoid type of cutaneous tuberculosis (with positive bacillary findings) has been the source of much confusion. We believe this point deserves considerable emphasis. It, for example, explains the positive findings in most of the cases compiled by Schröpl [14] (Table 2).

Summary of Bacterial Studies: The significance of finding tubercle bacilli in cases of sarcoidosis is summarized as follows:

1. With modern technic it is extremely rare to find tubercle bacilli. Out of 239 cases in which sarcoid tissue was inoculated into guinea pigs and a variety of other animal species or implanted on culture media, there were no positive findings. In 26 additional cases one inoculation was positive, and one culture was positive. It is not known whether these two cases had concomitant frank tuberculosis. Of Schröpl's 10 cases included in Table 2, it is believed that one was a case of avian tuberculosis, four were definite cases of cutaneous tuberculosis with a sarcoid architecture, and one was a questionable case of cutaneous tuberculosis with a sarcoid architecture. In three cases there was not enough information to arrive at a decision. One case might have been sarcoidosis.

2. When tubercle bacilli have been found, there nearly always has been a flaw in the demonstration. The flaw has been either bacteriologic or diagnostic.

Thus, the second point advanced in the favor of a tuberculous etiology, namely, the occasional finding of tubercle bacilli, is seen to have little, if any, value in explaining the etiology of sarcoidosis.

Relative Anergy Against Tuberculin.—The final point mentioned under the arguments in favor of a tuberculous origin was the relative anergy to tuberculin which a high percentage of the individuals with sarcoidosis display. This fact, in conjunction with the belief that the condition is a tuberculous one, is the basis for the Jadassohnian theory of positive anergy, a concept which will be dealt with in detail at a later point in this paper. Suffice it to say now that in my opinion there is little if any evidence to support such a hypothesis, and the altered reactivity can be explained adequately on other grounds.

ARGUMENTS AGAINST A TUBERCULOUS ORIGIN

Turning now to the arguments which seem to be against a tuberculous origin for this condition, I admit in advance that none of the arguments which will be advanced are crucial. Yet, in each case they are against a tuberculous basis, and, while the individual points can be countered, this requires in each instance a further series of hypotheses or assumptions, which, while not disproved, are totally unfounded and in some cases contrary to known facts. To me these arguments total up to an impressive weight of evidence against the tuberculous origin.

The arguments will be considered under three headings, namely, (1) pathologic arguments, (2) immunologic and bacteriologic arguments, and (3) epidemiologic arguments.

Pathologic Arguments

There are some resemblances between the pathologic lesions of sarcoidosis and those of true tuberculosis, but, as R. Bodley Scott [19] felicitously stated, "Most pathologists would admit that the histological signature of the tubercle bacillus is susceptible of forgery . . ." Actually there are important differences between the two which are related below.

Lindau,[6] despite the fact that he favored the tuberculous origin, stated, ". . . and the systemic distribution of the lesions in benign lymphogranulomatosis constitutes a striking feature which does not resemble tuberculosis with its irregularly distributed localizations."

Rich [18n] stated, "Tuberculosis of the myocardium is decidedly unknown, whereas in sarcoid the myocardium is frequently involved, and may be so massively infiltrated that heart failure results." Rich also went on to state that ". . . the lungs may be peppered with miliary-sarcoid tubercles with practically no involvement of the spleen and liver—a condition that never occurs in miliary tuberculosis."

Fisher [20] pointed out that the marked splenomegaly commonly encountered in sarcoidosis is almost never seen in tuberculosis.

Freiman,[21] in discussing the various kinds of inclusion bodies seen in sarcoidosis, stated, "All of them appear to be nonspecific and are without known significance, but it is of interest that they have not been observed in association with unequivocally tuberculous lesions in man."

Rich also in referring to inclusion bodies remarked, ". . . which are never encountered in unequivocally tuberculous lesions in man or the ordinary laboratory animals."

The final pathologic argument, which to me is a very impressive one, is the fact that one can find side by side typical sarcoid tubercles and large caseating tuberculous lesions, the former without caseation and without bacilli, the latter teeming with bacilli (Pappenheimer,[22] Carnes [23]). It is difficult to understand how sarcoidosis can be a manifestation of an altered immunologic response to the tubercle bacillus when one has at one place a sarcoid lesion and a few millimeters away an ordinary tuberculous lesion indicating a usual type of hypersensitivity reaction on the part of the host to the tubercle bacillus.

Autopsy Studies in Sarcoidosis.—It is, I think, obvious that autopsy studies should furnish some information on the relationship of tuberculosis and sarcoidosis. Rubin and Pinner [5] in 1944 made a thorough search of the literature and reported on 44 cases of sarcoidosis in which autopsies had been done. The authors in

19. Scott, R. B.: Sarcoidosis of Boeck, Brit. M. J. **2**:777, 1938.

20. Fisher, A. M.: Sarcoidosis, in Myers, J. A., and McKinlay, C. A.: The Chest and the Heart, Springfield, Ill., Charles C Thomas, 1948, vol. 1, p. 609.

21. Freiman, D. G.: Medical Progress: Sarcoidosis, New England J. Med. **239**:664, 709 and 743, 1948.

22. Pappenheimer, A. M., in discussion on Carnes, W. H., and Raffel, S.: Serologic Reactions of Patients with Sarcoidosis to Antigens of Mycobacterium Tuberculosis, Am. J. Path. **24**:697, 1948.

23. Carnes, W. H., in discussion on Carnes and Raffell, Am. J. Path. **24**:697, 1948.

closing said, "The present series of cases does not seem to add anything essential to the solution of the etiological question." Hogan,[1] writing in 1946, made this statement:

> In the overwhelming majority of sarcoid patients it is impossible to hold to tuberculosis as the whole disease or any part of it. This is true in the larger portion of autopsies. Hence in the total of 44 autopsies in the literature (including the one presented in this series) the presence of active tuberculosis or of tubercle bacilli was detected in 11, or 25 per cent, of the cases, and in only 5, or 11 per cent, was tuberculosis the cause of death. Certainly if the tubercle bacillus were the etiological agent it is not conceivable that it could remain undetected in cases such as the second of this series where there was widespread destruction of tissue and where a more than adequate search with multiple methods proved fruitless.

Rosenthal and Feigin [13r] in 1948 added four more cases on which autopsies had been done and commented concerning their cases, "Tuberculosis was neither a major nor a contributory cause of death in any of the cases." Ustvedt,[24] in reviewing the significance of the autopsy findings, remarked as follows:

> The workers who advance the theory that sarcoid is a non-caseating phase of haematogenous tuberculosis stress the frequency with which sarcoid is complicated by or, as Pinner puts it, changed to caseating tuberculosis. From the autopsy material it seems to be doubtful if tuberculosis is more often the cause of death in sarcoid than in individuals of the same age without sarcoid. In the 59 cases which I have collected (58 from the literature and one of my own), tuberculosis was found to be the cause of death eleven times. The cases originate from a series of different countries and from all age-groups. It is therefore impossible in so small a number of cases to say anything definite as to the probability of fatal tuberculosis under "normal circumstances." About the half of the patients were less than forty years old at the time of death; 18% deaths of tuberculosis does not seem very high, but an adequate comparison is not possible.

Finally, Ricker and Clark [13p] in 1949 reported on 22 additional autopsies. Tuberculosis was listed as the cause of death in two of the cases.[25] Adding these to Ustvedt's 59 gives a total of 81 cases of sarcoidosis on which autopsies were done, with tuberculosis as the cause of death in only 13, or 16%, which adds more weight to Ustvedt's point.

In summing up the information derived from the autopsy studies, the most one can say is that no evidence is offered for a tuberculous cause, and in the opinion of some, this lack of evidence argues strongly against such a cause.

Immunologic Arguments

Theory of Positive Anergy.—It is generally agreed that people with sarcoidosis display a reduced cutaneous reactivity to tuberculin.[26] Now, if the condition

24. Ustvedt, H. J.: Autopsy Findings in Boeck's Sarcoid, Tubercle **29**:107, 1948.

25. It probably is not quite statistically fair to incorporate all 22 of Ricker and Clark's cases, since the cause of death in six was accidental (wounds, suicide); consequently, if the six subjects had lived, fatal tuberculosis might have developed in some of them.

26. It might also be pointed out that persons with Hodgkin's disease or mycosis fungoides have an extreme degree of anergy toward tuberculin. (Dubin, I. N.: The Poverty of the Immunological Mechanism in Patients with Hodgkin's Disease, Ann. Int. Med. **27**:898, 1947. Rottino, A., and Hoffmann, G. T.: Studies of Immunological Reactions of Patients with Hodgkin's Disease: The Tuberculin Reaction, Am. J. M. Sc. **220**:662, 1950.) While I do not believe that the cases of mycosis fungoides have been too completely studied from this point of view, Hodgkin's disease has been studied in great detail, and it would appear that in all respects the reaction toward tuberculin or to the tubercle bacillus is the same in these people as in persons with sarcoidosis.

is on a tuberculous basis, how can one explain the relative anergy to tuberculin? Ordinarily, when a person fails to give a positive skin reaction to an antigen, one comes to one of three conclusions: (1) He has never become sensitized to the antigen; (2) he is moribund, and because of this incapable of reacting, or (3) he is suffering from an intercurrent illness which causes a depression of cutaneous reactivity. Such forms of nonreactivity have been collectively labeled negative anergy. In the case of sarcoidosis the first explanation could not apply, inasmuch as it is hypothesized that the disease is on a tuberculous basis. The second explanation is not relevant in the majority of cases, inasmuch as the patients are ordinarily in fair health. The third explanation is one which could apply but, for reasons that are not clear to me, has never been seriously entertained. Possibly the reason for this is that the usual infectious condition in which cutaneous reactivity to tuberculin is depressed are accompanied with fever and are of a rather transient nature. Since sarcoidosis is a rather protracted ailment and, as a rule, afebrile, the anergy accompanying it was not considered to belong to this category. It is also asserted that the depression of reactivity in the exanthems, specifically measles, is not specific for tuberculosis, for in it most forms of cutaneous reactivity are depressed, whereas in sarcoidosis the anergy is limited to tuberculosis. It should be pointed out that, while in measles the depression of reactivity is certainly not specific for tuberculin, there is no valid evidence to show that such is the case in sarcoidosis.

J. Jadassohn hypothesized [27] that the lack of reactivity on the part of people with sarcoidosis was due to the fact that they destroyed the tuberculin or products formed from it in the body so rapidly that the sensitized cells had no chance to react. This form of lack of reactivity he termed positive anergy, in contradistinction to the previously described negative forms of anergy. As has already been mentioned, it is asserted that the positive anergy of sarcoid is specific for tuberculin. To my knowledge there has not been any systematic study of the effect of the development of sarcoidosis on preexisting allergic reactions or of the ability of persons with this disease to develop new sensitizations. The few observations on these lines have, in general, indicated that the reduction of sensitivity is not limited to tuberculin. For example, in studies of sarcoidosis in Negroes it would

27. "Der organismus wird nämlich (um es grob auszudrücken) mit dem Tuberkulin so rasch fertig, dass es nicht oder nur zu einer schwachen Reaktion kommt. Im Gegensatz zu dieser Form der Anergie, die als spezifische oder positive bezeichnet wurde, und die eine besondere Form der Immunität darstellt, kommt es bei der negativen Anergie bei nicht infizierten oder bei Kachektischen nicht zur Reaktion, weil der Organismus nicht mit dem Tuberkulin zu reagieren vermag." [To express it crudely, the organism is able to deal with tuberculin so quickly that no reaction, or only a weak reaction, ensues. In contrast to this type of anergy, which has been designated specific or positive and which represents a special form of immunity, in the presence of negative anergy a reaction is not produced in a noninfected or cachectic person because the organism is unable to react with tuberculin.] (Jadassohn, W., cited by Lemming, R.: An Attempt to Analyze the Tuberculin Anergy of Schaumann's Disease [Boeck's Sarcoid] and Uveoparotid Fever by Means of BCG Vaccination, Acta med. scandinav. **103**:400, 1940; quoted by Jadassohn, W.: Die Immunbiologie der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtekrankheiten, Berlin, Julius Springer, 1932, Vol. 2, p. 367.) Lemming, as well as Werner Jadassohn, when referring to positive anergy, gave the statement quoted above, but neither one was explicit as to the source. I have not been able to locate the original.

appear that a positive Wassermann reaction occurs less frequently in Negroes with sarcoidosis than in those from the same milieu without sarcoidosis.[28]

Let us consider for a moment the theory that in the person with positive anergy the tuberculin is so rapidly destroyed that it is not capable of provoking a reaction or of doing harm. First of all, it should be clearly realized that this is pure assumption. There is no experimental evidence of any sort to support it. As a matter of fact, the known immunological facts indicate that an immune animal, while capable of destroying the offending organism, does not do so in the extremely rapid fashion intimated by Jadassohn, and this is especially so for the tubercle bacillus, as the following quotation from Rich[29] shows:

> For example, if a measured number of pneumococci are introduced into the skin in a series of immunized and control animals, and if sites of inoculation are removed from animals of each group immediately and at intervals thereafter, one can, by staining the histological sections for bacteria, follow with ease and precision the progressive multiplication of the bacteria in the lesions of the non-immune animals and the phagocytosis, intracellular destruction and, within 24 to 48 hours, the complete and permanent disappearance of the bacteria in the lesions of the immunized animals (618); and this direct visual evidence can readily be confirmed by culturing the lesions at intervals. When tubercle bacilli are used in an experiment of this type, however, in numbers not large enough to cause a sloughing, hypersensitive reaction with loss of bacilli from the ulceration, little difference may be seen in the number of stainable bacilli in the lesions of the immunized and control animals during the first day or two, but how many of the stainable bacilli may be dead bacilli no one can say. Then the bacilli in the lesions of the control animals begin to become more numerous because of their unrestricted multiplication, but still there may be little difference in the number of stainable bacilli in the lesions of the immunized animals as compared with the number originally deposited at the site. With the further lapse of time the number of bacilli in the control animals increases greatly, but still the number in the immunized animals may show no clear cut decrease. Indeed, there may even be a moderate increase in their numbers, though not nearly so great an increase as in the control lesions.

Further evidence on this point was furnished by Freund and Angevine.[30] The conclusions of their article are as follows:

> 1. Tubercle bacilli injected into the skin of animals immunized by heat killed tubercle bacilli multiply within the first few days after injection *and are after the same intervals more abundant than in infected animals that were previously normal* [italics mine].
>
> 2. With superficial necrosis many tubercle bacilli may be discharged when sloughing occurs.
>
> 3. Tubercle bacilli introduced into the skin of immunized animals that are hypersensitive and have formed antibodies, reach the draining lymph nodes from 2 days to 2 weeks later than those similarly injected into normal animals.
>
> 4. Tubercle bacilli multiply actively at the site of injection during the period of retarded lymphatic dissemination; hence the retardation is caused by local fixation and not by destruction of tubercle bacilli.

It is thus seen that in the immunized animal there is no evidence for rapid destruction and that there is more than ample opportunity for a reaction to take place.[30a]

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28. (*a*) There appear to be studies in progress bearing on these points. (*b*) Israel, H. L.; Sones, M.; Stein, S. C., and Aronson, J. D.: BCG Vaccination in Sarcoidosis, Am. Rev. Tuberc. **62**:408, 1950.

29. Rich.[13o] The number 618 in the following quotation is a reference in Rich's text, which is Rich, A. R.; Jennings, F. B., Jr., and Downing, L. M.: The Persistence of Immunity After the Abolition of Allergy by Desensitization, Bull. Johns Hopkins Hosp. **53**:172, 1933.

30. Freund, J., and Angevine, D. M.: The Spread of Tubercle Bacilli in the Bodies of Sensitized and Immunized Animals, J. Immunol. **35**:271, 1938.

30a. Together with Drs. Senear, Haeberlin, Szymanski, and Brebis, I have found that intracutaneously implanted tubercle bacilli (BCG) have persisted in situ and remained viable for at least 12 days. (Unpublished observations.)

Implicit in the Jadassohn hypothesis is the assumption that, because a cutaneous reaction is not seen at the site of the tuberculin inoculation, no reaction is present. It is further assumed that because the skin behaves in this fashion all the tissues will. Let us examine the validity of these assumptions.

1. It has been shown by Schaumann and Seeberg [31] that at the site of a so-called negative tuberculin test in sarcoidosis one finds on histologic examination a reaction, or, in other words, the patient is in reality reacting towards the tuberculin.

2. It is entirely erroneous to suppose that, because a person exhibits no cutaneous reactivity toward an antigen (assuming this to be the case), the internal viscera will not react to the same antigen. There are many examples of this in the immunologic literature. One or two will suffice to illustrate the point. Freund [32] showed that very young guinea pigs which had been sensitized to tubercle bacilli would fail to yield a cutaneous tuberculin reaction—yet would die of a systemic tuberculin effect if the tuberculin were given intraperitoneally. Hehre and Freund [33] showed that rats infected with tubercle bacilli, even though they did not exhibit a cutaneous reaction to tuberculin, still were killed by the intraperitoneal administration of tuberculin, or, in other words, there was a systemic sensitivity toward tuberculin. It should also be pointed out that a failure to react to tuberculin does not necessarily mean that there will not be a reaction to the tubercle bacillus (Freund and Angevine, [30] Thomassen [34]).

Heilman and Feldman [35] have shown that visceral cells from animals which failed to give a skin reaction to a given antigen because of an intercurrent infection or because the animal was moribund were nevertheless killed when exposed to the same antigen in vitro. Thus, the fact that a patient with sarcoidosis fails to yield a cutaneous reaction to tuberculin (assuming this to be so) is no sign that his internal viscera will not react, as indeed they must if the condition is on a tuberculous basis, or why the lesions?

For these various reasons it is seen that there is no evidence to support the original Jadassohn theory of a rapid destruction of the tuberculin, and indeed there exists a considerable body of fact contrary to it.

Students of Jadassohn, especially Martenstein,[36] have altered Jadassohn's views somewhat. They believe that the chief reason for the lack of reaction in patients with sarcoidosis is the presence of a circulating antibody which they term an "anticutin." This antibody has the property when mixed with tuberculin of impairing the ability of the tuberculin to produce a cutaneous reaction in a hypersensitive

31. Schaumann, J., and Seeberg, G.: On Cutaneous Reactions in Cases of Lymphogranulomatosis Benigna, Acta dermat.-venereol. **28**:158, 1948.

32. Freund, J.: The Sensitiveness of Tuberculous Guinea Pigs 1 Month Old to the Toxicity of Tuberculin, J. Immunol. **17**:465, 1929.

33. Hehre, H., and Freund, J.: Sensitization, Antibody Formation and Lesions Produced by Tubercle Bacilli in the Albino Rat, Arch. Path. **27**:289 (Feb.) 1939.

34. Thomassen, O. K.: The Connexion Between Tuberculin Allergy and Tubercle Bacillus Allergy: Clinical and Experimental Investigations, Acta tuberc. scandinav. **21**:87, 1947.

35. Heilman, D. H., and Feldman, W. H.: Specific Cytotoxic Action of Tuberculin, Am. Rev. Tuberc. **54**:312, 1946.

36. Martenstein, H.: Wirkung des Serums von Sarkoid-Boeck- und Lupus-pernio-Kranken auf Tuberkulin, Arch. Dermat. u. Syph. **136**:317, 1921; Sarkoid Boeck und Lupus pernio, ibid. **147**:70, 1924.

subject. It might be pointed out that anticutins were described as long ago as 1908 by Pickert and Löwenstein,[37] but it should be realized that the existence of such antibodies has never been generally agreed upon. It is indeed questionable whether they are antibodies in the usual meaning of that term. Since the work of Martenstein, the rather limited number of studies which have been done in an effort to find anticutins in sarcoidosis have been inconclusive or negative. Pinner, Weiss, and Cohen[38] failed to establish any correlation between the presence of anticutins on the one hand and the existence of tuberculin anergy on the other. Rubin and Pinner[5] (1944) came to the following conclusion: "We do not believe that anticutins play a significant immunologic role in sarcoidosis; their occurrence is neither diagnostic nor pathognomonic."

Later work (1949) by Wells and Wylie[39] indicates that a tuberculin-neutralizing factor is present in the serum of many patients with sarcoidosis during certain stages of the disease but that the serum of patients with other diseases having as a pathological feature the mobilization of epithelioid cells—e. g., kala-azar —may contain a similarly potent tuberculin-neutralizing factor.[40] They, incidentally, believe this factor is different from the anticutin of Pickert and Löwenstein. It is important to realize that, even though in cases of sarcoidosis there may be a tuberculin-neutralizing factor, this in no way proves the theory of positive anergy. The existence of such a material would, of course, be consonant with the theory, but its presence does not add positive weight to the theory.

The proof of the theory of positive anergy requires the demonstration that after exposure to the antigen (tubercle bacillus) the body can develop an immunologic state which is characterized by (*a*) the development of "sarcoid-type" lesions on exposure to the antigen (tubercle bacillus or its derivatives), (*b*) a relative degree of cutaneous inertness (anergy) to the same antigens, and (c)[41] a relative resis-

37. Pickert, M., and Löwenstein, E.: Einer neue Methode zur Prüfung der Tuberkulin-immunität, Deutsch. med. Wchnschr. **34**:2262, 1908.

38. Pinner, M.; Weiss, M., and Cohen, A. C.: Procutins and Anticutins, Yale J. Biol. & Med. **15**:459, 1943.

39. Wells, A. Q., and Wylie, J. A. H.: A Tuberculin-Neutralising Factor in the Serum of Patients with Sarcoidosis, Lancet **1**:439, 1949.

40. To me the term "tuberculin-neutralizing factor" is a better term for the substance in the serum than the term "anticutin," because the prefix "anti" gives the implication that the anticutin is of the nature of an antibody which the host develops in response to the antigen (tubercle bacillus) and has a specificity directed against it. There is no evidence bearing on the latter point. It is my opinion that the property of tuberculin neutralization exhibited by serums from some patients with sarcoidosis (and other conditions) arises adventitiously as a result of the changes in the serum proteins found in these conditions. The substance which has this property is probably not an antibody manufactured by the host in response to the tubercle bacillus (or derivatives of it) with a specificity against that antigen. The tuberculin-neutralizing material was found by Wells and Wylie to be in the gamma globulin fraction of the serum; consequently, it may be an antibody against some other microorganism which for reasons unknown has this tuberculin-neutralizing property. Such a hypothesis is discussed in more detail in a later section.

41. Historically, it is only fair to state that the advocates of this hypothesis put forth their views when sarcoidosis was regarded as a much more benign condition than it now is. To me it is very doubtful whether anyone today would consider that a patient with sarcoidosis, assuming the condition to be tuberculous, had an enhanced resistance toward the tubercle bacillus. In a series of 43 patients, Fisher[20] had almost a 12% mortality, and, adding to this any incapacitation which the patients with nonfatal disease may have had, the designation "benign" surely seems inappropriate.

tance toward the ravages of the tubercle bacillus. It is possibly superfluous to state that these proofs have never been advanced.

Work in the Rat and Its Meaning: In an effort to support the theory of positive anergy, analogies were made between the reaction of the white rat to the tubercle bacillus and sarcoidosis (Werner Jadassohn [42]). It had been noted for many years that the rat behaves in a different fashion from most species toward the tubercle bacillus: (1) When the rat is inoculated with virulent tubercle bacilli sarcoid-like lesions develop; (2) the rat fails to attain tuberculin positivity, and (3) the serum of the rat contains, according to W. Jadassohn, tuberculin-neutralizing substances. It was therefore argued that here was a model of positive anergy. The rat, for reasons unknown, had "normal anticutins" which prevented it from giving a positive tuberculin reaction, and presumably the same reasons also caused the animal to exhibit sarcoid-like lesions rather than classic caseation tuberculosis.

Let us examine the strength with which these findings support the Jadassohn theory of positive anergy. First, what conclusions can be drawn from the behavior of one species toward an organism regarding the likely behavior of another species toward that organism? In general, this is a rather hazardous procedure and especially so with the rat, which, as is well known, often reacts immunologically differently than many other animals.

Second, are the findings in the rat identical with those in patients with sarcoid? It is admitted by all workers (Gloyne and Page,[43] Hehre and Freund,[86] Jadassohn and Feldman and Karlson [44]) that numerous tubercle bacilli can be found in the lesions. This constant finding of the organism in the lesions of the rat has no counterpart in human sarcoidosis. Jadassohn thought that the organisms had been morphologically altered and that this indicated degeneration. Feldman and Karlson do not make this point. Gloyne and Page recovered virulent tubercle bacilli from the tissues as late as several months after inoculation. Hehre and Freund stated,

> We have found that the tubercle bacilli induce the formation of tubercles and that the micro-organisms are in epithelioid and giant cells. The number of micro-organisms in these cells is moderate in most of the rats, but tubercle bacilli in immense numbers were seen in the lungs of 4 rats that died one, six, twelve and eighteen months after infection. In most instances, though the disease has failed to progress, tubercle bacilli have persisted, and in a few animals they have undergone active multiplication and are found in great numbers within epithelioid and giant cells.

It is thus apparent that there is no evidence for the destruction or attenuation of the bacilli as postulated by the hypothesis of positive anergy.

While it it generally agreed that the rat gives a sarcoid-like reaction to inoculation with tubercle bacilli, it is not generally admitted that rat serum has tuberculin-neutralizing properties. Pinner, Weiss, and Cohen [88] in a study of serums from 11 rats failed to find anticutins in any of them.

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42. Jadassohn, W.: Die Inokulationstuberkulose der Rattenhaut, Arch. Dermat. u. Syph. **167**:169, 1932.

43. Gloyne, S. R., and Page, D. S.: The Reaction to B. Tuberculosis in the Albino Rat, J. Path. & Bact. **26**:224, 1923.

44. Feldman, W. H., and Karlson, A. G.: Experimental Intracutaneous Tuberculosis in the White Rat, J. Invest. Dermat. **3**:107, 1940.

Even if the serum of the rat possessed anticutins as measured by its ability to reduce the tuberculin reaction in some other species, the serum does not furnish any protection for another species, inasmuch as Gloyne and Page found that repeated injection of rat serum into guinea pigs inoculated with tubercle bacilli did not affect the outcome of the disease. It would not, therefore, appear that the work on the rat affords any evidence for the theory of positive anergy.

Actually, much of this discussion is academic and meaningless if the work of Kallós[45] is corroborated. Kallós has produced evidence which indicates that the white rat behaves toward the tubercle bacillus in this rather abnormal fashion because of the presence of a latent Bartonella infection, which he believes so stimulates the reticuloendothelial system of the animal that it is able to withstand other organisms, such as the tubercle bacillus. Kallós found that if the Bartonella infection was cured and the spleens of these animals then extirpated and if the rats were then inoculated with tubercle bacilli, the usual caseation type of tuberculosis developed.

Studies with BCG Inoculations in Sarcoidosis: More recently, in an attempt to elucidate the nature of the tuberculin anergy exhibited by patients with sarcoidosis, BCG inoculations have been employed. This work was introduced by Lemming[46] and has subsequently been carried on by a number of workers. The following points have been asserted: 1. The intracutaneous inoculations of BCG into persons with sarcoidosis yield local lesions which have a somewhat different appearance from those which ordinarily develop when BCG inoculations are done in persons who have not been exposed to the tubercle bacillus and are consequently tuberculin negative. Also, the histologic structure of the lesions induced in the sarcoid group is said to be that of sarcoidosis rather than that of classic tuberculosis, which ultimately develops in the other group. 2. A tuberculin-negative person, who so far as is known has not been previously exposed to the tubercle bacilli, when inoculated with BCG, converts to tuberculin positivity in a high percentage of cases; whereas in sarcoidosis this is not the case. In the majority of inoculated persons either there is no conversion to tuberculin positivity or if there is a conversion the sensitivity is poorly maintained.

Lemming believed that these results strongly argued for the theory of positive anergy of Jadassohn. To me such a conclusion is unwarranted. All that can be said is that persons with sarcoidosis on the whole react differently to inoculations with BCG than do those who react negatively to tuberculin because they apparently have not been previously exposed to the tubercle bacillus. The experiments, however, shed no light on the mechanism or the nature of the difference. It might be pointed out that, according to de Marval,[47] patients with Hodgkin's disease react in an identical fashion toward BCG inoculation as do those with sarcoidosis.

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45. Kallós, P.: Beiträge zur Immunbiologie der Tuberkulose, Hasse W. Tullbergs Förlag, Stockholm, 1941, p. 93.

46. Lemming, R.: An Attempt to Analyze the Tuberculin Anergy in Schaumann's Disease (Boeck's Sarcoid) and Uveoparotid Fever by Means of BCG Vaccination, Acta med. scandinav. **103**:400, 1940.

47. de Marval, L., cited by Dubin, I. N.: The Poverty of the Immunological Mechanism in Patients with Hodgkin's Disease, Ann. Int. Med. **27**:898, 1947.

I should like to conclude my comments concerning the interpretation of the results of BCG vaccination with a quotation from Israel and his associates [48]:

> There seems to be no substantial basis for considering the formation of sarcoid-like lesions at the site of BCG vaccination indicative of a specific etiologic relationship of tuberculosis and sarcoidosis. In our experience, the behavior of the gross local lesion in the majority of sarcoid patients is indistinguishable from that observed in controls. The epithelioid, sarcoid-like reactions which have been observed histologically following BCG vaccination (2) are also produced by inoculation of Kveim antigen and extracts of normal splenic tissue (12). This suggests that in sarcoidosis there is a characteristic inflammatory reaction to a number of related or unrelated substances.
>
> It has been demonstrated that a similar tissue reaction may occur as the result of exposure to beryllium fumes or infection with certain mycotic and bacterial organisms. Thus, from the study of local reactions as well as skin sensitivity to tuberculin following BCG vaccination, the changes observed are explicable on the basis of a nonspecific alteration of general immunologic mechanisms produced by causative agents, only a few of which as yet have been identified. The possibility that tubercle bacilli may be one of these causative factors is not excluded by the results of this investigation, but it is difficult in view of the evidence which we have presented to construe anergy to tuberculin as evidence for a tuberculous etiology. The assumption that the tuberculin anergy observed in this disease is specific has been a basic one in the hypothesis that sarcoidosis represents an atypical form of tuberculosis. The demonstration that the anergy is nonspecific thus tends to weaken the case for a tuberculous etiology of this disease. It may safely be concluded that tuberculin anergy does not deserve the emphasis it has received as a clue to the etiology of sarcoidosis.

Lurie and Zappasodi [49] have studied five inbred families of rabbits of known genetic resistance to tuberculosis. It was found that when they were inoculated with BCG they behaved differently. In the resistant animals the lesions at the site of inoculation grew rapidly, reached their peak, and then healed promptly. In the susceptible rabbits the lesions grew more slowly, achieved their height tardily, and healed slowly. In the resistant rabbits there was a rapider, and usually a more intense, development of tuberculin sensitivity. Now the patient with sarcoidosis behaves like the susceptible rabbit. One would think if there were such a thing as positive anergy it would cause such a patient to react in the fashion of the resistant animal.

Clinical Paradox Arising from the Theory of Positive Anergy: Let us consider the ordinary person who has been exposed to the tubercle bacillus. He betrays by radiologic evidence signs of this encounter. He is also ordinarily allergic (hyperergic) to tuberculin, but he does not have clinical tuberculosis. Let us now consider the person with sarcoidosis: According to the theory of positive anergy, he has an enhanced ability to handle the tubercle bacillus—yet his system is riddled with lesions.

The theory of positive anergy puts us in the paradoxical situation of explaining that persons with tuberculous lesions (sarcoidosis) are those with enhanced immunity, whereas persons with no lesions, persons who have a positive reaction

48. The numbers in parentheses in the following quotation are references given by Israel.[28b] Reference (2) is Lemming, R.: Development of Boeck's Sarcoid at the Place on the Skin Where BCG Vaccination Had Been Made in a Case of Schaumann's Disease, Acta méd. scandinav. **110**:151, 1942. Reference (12) is Nelson, C. T.: Observations on Kveim Reaction in Sarcoidosis of American Negro, J. Invest. Dermat. **10**:15, 1948.

49. Lurie, M. B., and Zappasodi, P.: Response to BCG as an Index of Genetic Resistance to Tuberculosis, Federation Proc. **9**:386, 1950.

to tuberculin but have no clinical manifestation of tuberculous infection, are those who do not have an enhanced resistance.

We have dealt at some length with the theory of positive anergy because we feel it is a theory that has wrongly dominated much of the immunologic thinking in this field.[50] It has neither theoretical foundation nor experimental verification.

Other Immunologic Arguments Against Tuberculous Etiology.—If this disease were on a tuberculous basis, surely one would expect to find some sort of immunologic evidence that the host had reacted to the tubercle bacillus. Carnes and Raffel,[13c] in a very careful, detailed study looking for the presence of complement-fixing antibodies against the tubercle bacillus or derivatives of it, reported these findings: 1. Persons with sarcoidosis exhibit such antibodies in statistically significantly less numbers than do persons with proved tuberculosis. 2. Persons with sarcoidosis exhibit such antibodies in no greater incidence than do normal persons who give a positive tuberculin reaction and who do not have any clinical evidence of tuberculosis. 3. Persons with sarcoidosis exhibit such antibodies in a higher percentage than do normal persons who give no evidence, immunologically or clinically, of ever having been exposed to the tubercle bacillus. To sum up, then, Carnes and Raffel found that persons with sarcoidosis, so far as complement-fixing antibodies to tuberculoprotein and other derivatives of the tubercle bacillus are concerned, behaved in the same way as the majority of the population who give immunologic evidence of having been exposed to the tubercle bacillus but who have no clinical evidence of the disease. In all forms of proved tuberculosis studied, complement-fixing antibodies were found in a significantly higher titer than in sarcoidosis. It would seem if this disease is on a tuberculous basis that either the sufferers from it would react as all other examples of proved tuberculosis do, or, assuming the validity of the theory of positive anergy, this protective mechanism would cause them to react as little as do persons who had never met the tubercle bacillus. Yet, neither of these was found to be the case. It seems to me that this is a potent argument against the tuberculous origin of the disease.

One final immunologic argument against a tuberculous causation is that Rothbard and his associates[51] have found that the hemagglutination reaction of Middlebrook and Dubos is negative with serums from persons with Boeck's sarcoidosis. This reaction is known to be highly specific for active tuberculosis.

Significance of the Kveim Reaction: Kveim has shown, and it has subsequently been confirmed, that patients with sarcoidosis often exhibit a local reaction to the intracutaneous injection of heated saline suspensions of tissues obtained from persons with active sarcoidosis. The theory of the test is that the diseased tissues from patients with active disease contain the etiologic agent or antigenic fractions derived from it. Such a material when introduced intracutaneously into other persons with the disease should elicit a reaction. Regardless of the validity of the above hypothesis, which need not concern us here, it will be my purpose to see what information this test furnishes about the etiology of sarcoidosis. It has been shown by several workers that the Kveim antigen does not ordinarily produce

50. In this connection it might not be amiss to quote from Cicero, who said, "The authority of those who teach is often an obstacle to those who want to learn."

51. Rothbard, S.; Dooneief, A. S., and Hite, K. E.: The Practical Application of a Hemagglutination Reaction in Pulmonary Tuberculosis, J. Clin. Invest. **29**:842, 1950.

a reaction when injected into persons with systemic tuberculosis or with lupus vulgaris.

It would be thought that if the Kveim antigen contains antigenic material and if this antigenic material is the tubercle bacillus or a derivative of it the antigen would yield a reaction in known tuberculous patients, but, as already stated, it does not ordinarily do so. We can, then, only come to the conclusion that, while the Kveim reaction does not shed any light in a positive way on the etiology of sarcoidosis, it seems to be another bit of evidence against a tuberculous causation.

Sarcoidosis and Erythema Nodosum: Sarcoidosis may start with an erythema nodosum (Kerley,[52] Forssman,[53] Löfgren,[54] and Bjerkelund[55]). Now, it is a well established fact that erythema nodosum is an initial manifestation of the development of a sensitization to some allergen. In all cases in which the allergen is definitely known, at the time of the appearance of the erythema nodosum the patient is hypersensitive to the allergen. This has been especially well worked out in the type of case in which erythema nodosum is an initial manifestation of tuberculosis. Skiöld[56] stated, "Erythema nodosum associated with tuberculosis is characterized by intense sensitivity of the skin to tuberculin." Heimbeck[57] stated, "E. N. [erythema nodosum] commonly indicates a maximum reaction." This was said with reference to the strength of the tuberculin reaction in cases of erythema nodosum. Now, the patients with sarcoidosis which began with an erythema nodosum were anergic when tested with tuberculin. If the tubercle bacillus is the cause of sarcoidosis, then at the time the erythema nodosum makes its appearance the development of sensitivity to the tubercle bacillus and/or its products should be reaching its height; yet, as was just mentioned, the tuberculin reaction was negative. This, unless we make new and totally unsupported immunologic hypotheses, would indicate that the erythema nodosum in sarcoidosis is evidence of allergization to an agent other than the tubercle bacillus.

Epidemiologic Arguments

If sarcoidosis were on a tuberculous basis, it would be expected that it would originate more frequently in homes where tuberculosis exists than is apparently the case. Longcope and Pierson[58] in this connection state that the disease rarely occurs in tuberculous families. There is no evidence to the effect that sarcoidosis arises more frequently by virtue of contact with persons with known tuberculosis than it does where there is no history of this. Riley[4] remarked apropos of this point

52. Kerley, P.: The Significance of the Radiologic Manifestation of Erythema Nodosum, Brit. J. Radiol. **15**:155, 1942; Etiology of Erythema Nodosum, ibid. **16**:199, 1943.

53. Forssman, O.: Tuberculin-Negative Cases of Erythema Nodosum or Erythema Exsudativum Multiforme, Acta med. scandinav. **126**:393, 1946.

54. Löfgren, S.: Erythema Nodosum: Studies on Etiology and Pathogenesis in 185 Adult Cases, Acta med. scandinav., supp. 174, p. 1, 1946.

55. Bjerkelund, C. J.: Boeck's Sarcoid with Erythema Nodosum as an Initial Symptom: Report of Case, Acta med. scandinav. **128**:538, 1947.

56. Skiöld, N.: Erythema Nodosum: A Study of Its Clinical Features and Origin, Acta med. scandinav., supp. 157, p. 1, 1945.

57. Heimbeck, J.: The Significance of Erythema Nodosum Tuberculosum, Acta tuberc. scandinav. **24**:388, 1950.

58. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223, 1937.

The incidence of significant tuberculous contacts has been low in this series. Among 47 cases in which it was specifically determined, 6, or 13%, gave a positive history. In several of these the intimacy of the contact was not determined. Most series have shown a similar low incidence, although Hagn-Meincke, in a review of 26 cases reported a history of contact in one-half of his patients.

(What Hagn-Meincke [59] actually said was, ". . . . for half of our patients had tuberculous relatives and acquaintances, or they had been in contact with tuberculous persons in their work." This to me does not mean there was necessarily any intimacy of contact.) Similarly, if sarcoidosis were on a tuberculous basis one would expect that either tuberculosis or sarcoidosis would be more frequent in the other inhabitants of the home of a patient with this disease. Sarcoidosis occurring in siblings is sufficiently rare that it warrants reporting (Bickerstaff,[60] Robinson and Hahn [61]).

Geographically there are oddities in the distribution of sarcoidosis which do not correspond to similar data for tuberculosis. Michael and his associates,[62] in a study devoted especially to the epidemiologic aspects of sarcoidosis, have shown that in this country the disease occurs in significantly higher proportion in the southeastern corner of the country than elsewhere. Further, a disproportionate percentage of the cases occur in persons born in rural areas. Fisher [20] emphasizes that the overwhelming majority of the cases in the Johns Hopkins series came from the country or from small towns rather than from the city. Both the preponderance of cases in persons coming from rural areas and the higher incidence of cases in the southeastern corner of this country are contrary to the known epidemiology of tuberculosis. Similarly Lomholt [63] in Denmark found that most of his 49 cases came from the rural districts where tuberculosis was least common.

To sum up, then, my views concerning the tuberculous basis of sarcoidosis, I can only say that I believe it to be an improbable cause, and I agree wholeheartedly with the following statement by Michelson [64]:

Because of the frequency of a negative reaction in this disease to various dilutions of tuberculin, a tremendous amount of effort has been expended in exploring the so-called positive anergy and its significance concerning a tuberculous etiology. Granting that a negative reaction cannot be overlooked, nevertheless it appears to have been overemphasized to the exclusion of a possibly more fruitful search for the presence or absence of a bacillary cause. Few investigations have been directed along bacteriologic lines other than searches for the tubercle bacillus.

THE MULTIPLE FACTOR THEORY

Regarding the view that sarcoidosis is not an etiologic entity but that it can be caused by a variety of agents, it certainly would be a remarkable, almost fantastic, fact if a variety of unrelated micro-organisms could produce the

59. Hagn-Meincke, F.: Boeck's Sarcoid and Its Relation to Tuberculosis, Acta tuberc. scandinav. **18**:1, 1944.

60. Bickerstaff, E. R.: The Familial Aspects of Sarcoidosis, Brit. J. Tuberc. **43**:112, 1949.

61. Robinson, R. C. V., and Hahn, R. D.: Sarcoidosis in Siblings, Arch. Int. Med. **80**:249 (Aug.) 1947.

62. Michael, M. J.; Cole, R. M.; Beeson, P. B., and Olson, B. J.: Sarcoidosis: Preliminary Report on Study of 350 Cases with Special Reference to Epidemiology, Am. Rev. Tuberc. **62**:403, 1950.

63. Lomholt, cited by Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223, 1937.

64. Michelson, H. E.: Sarcoidosis: Review and Appraisal, J. A. M. A. **136**:1034 (April 17) 1948.

following combination of effects: (*a*) more-or-less-uniform widespread involvement in many and diverse viscera, yet with each of the hypothetical causes yielding changes in the same diverse organs; (*b*) uniform histologic changes in all of the involved tissues; (*c*) modification of the reactivity of the body in such a way as to impair its ability to respond to tuberculin and probably other antigens, and (*d*) bringing about of changes in the body such that none of the alleged causes are seen in, or isolated from, the tissues of the affected patients.

Regarding the so-called cases of sarcoidosis caused by the leprosy bacillus or the spirochete of syphilis, I believe it is more or less accepted that the cases of "sarcoidosis" for which these two are responsible are in reality "sarcoidosis-like" rather than conforming to the well-established classic picture of sarcoidosis shown by the cases in which no etiologic agent is found. Additional evidence against the causal role of these micro-organisms are the facts that sarcoidosis is relatively common in areas where leprosy is extremely rare or practically nonexistent and that the majority of patients show no clinical or serological evidence for syphilis.

COMMENT ON THE ETIOLOGY OF SARCOIDOSIS

This article has gone to considerable length to show why the concept of tuberculous origin is not tenable and in much less detail has pointed out the difficulties of the multiple etiologic concept, but it should be realized that certain of the arguments and findings, especially the negative bacteriologic ones, given against tuberculosis are applicable against any known infectious agent.

Thus, by exclusion one is more or less forced to the view that sarcoidosis is caused by a new infectious agent if it is an infection at all, and I believe that it is. There is some positive evidence to support this view in the recent work of Löfgren and Lundbäck,[65] who claim to have isolated a new virus belonging to the influenza-mumps-Newcastle-disease group of viruses from each of six cases of sarcoidosis on which the isolation was attempted.

Theoretical Explanations for Failure of Patients with Sarcoidosis to React to Tuberculin.—One of the chief arguments advanced by the proponents of the tuberculous origin is the relative anergy of many patients with sarcoidosis to tuberculin. It has been implied, if not explicitly stated, that this necessarily means some sort of immunologic response to the tubercle bacillus, and stemming from that is the belief that this organism must then be causally responsible. It has been shown that such a view is extremely improbable and that it has neither theoretical nor factual support. It therefore behooves us to consider other possible explanations for the tuberculin anergy. While, admittedly, any explanations in the present state of knowledge are purely hypothetical, they may serve some purpose in suggesting paths for future work.

It is a reasonably well-established fact that systematized sarcoidosis is a disease that involves the lymphoreticular structures of the body. In other words, there would appear to be a reticuloendothelial blockade in this disease. It is known that the experimental animal whose reticuloendothelial system is adequately blocked has an impaired ability to produce antibodies and to react to antigens (Cannon and

65. Löfgren, S., and Lundbäck, H.: Isolation of a Virus from 6 Cases of Sarcoidosis (Lymphogranulomatosis Benigna): Preliminary Report, Acta med. scandinav. **138**:71, 1950.

his associates,[66] Tuft [67]). Such, then, might be the situation with patients suffering from this condition, and it is indeed intimated by their failure to develop evidence of cutaneous hypersensitivity in response to BCG inoculation and skin sensitization or humoral antibodies in response to pertussis immunization. Kallós [45] has proposed that the reason the rat fails to develop a cutaneous hypersensitivity to tuberculin is because of the same mechanism, namely, a reticuloendothelial blockade.

As previously mentioned, there may be found in the serum of subjects with sarcoidosis a substance or substances which have tuberculin-neutralizing capacity. It is suggested that if this substance is an antibody it does not arise in response to the tubercle bacillus but rather as a result of stimulation by some other micro-organism. This would be analogous to the situation in various rickettsial diseases in which the micro-organismal antigen calls forth the production of agglutinins capable of reacting with Proteus OX19, an entirely unrelated organism (Weil-Felix reaction). On the other hand, the tuberculin-neutralizing material may not be an antibody in the conventional sense of the term but may rather correspond to an abnormal protein which develops during the course of sarcoidosis and which has this property. Such a situation is not without immunologic parallel. For example, it has been established that during the course of many acute infections caused by a variety of unrelated organisms there is elaborated a protein (found in the blood) which has the ability of reacting with the complex polysaccharide known as fraction "C" contained in the bodies of all pneumococci. It must be emphasized that many of the agents causing the diseases which call forth the production of the "C"-reacting protein do not themselves contain the "C" substance.[68] It is thus seen that there are other situations where an infection calls forth humoral substances which can react with products from micro-organisms unrelated to the etiologic agent of the infection.

SUMMARY AND CONCLUSIONS

Etiologic and immunologic concepts regarding sarcoidosis are reviewed.

The necessity for distinguishing between systematized sarcoidosis and the multiple-caused "reaction pattern" known as sarcoid is stressed.

It is concluded that the tuberculous causation of sarcoidosis is a most unlikely one.

It is concluded that it is extremely improbable that the disease arises on the basis of many diverse agents.

It is suggested that the most likely cause is a new infectious agent.

It is concluded that the "theory of positive anergy" has neither theoretical foundation nor experimental substantiation.

Theoretical arguments are given to explain the reason for the relative anergy to tuberculin displayed by many people with sarcoidosis.

1853 W. Polk St.

66. Cannon, P. R.; Baer, R. B.; Sullivan, F. L., and Webster, J. R.: The Influence of Blockade of the Reticulo-Endothelial System on the Formation of Antibodies, J. Immunol. **17**:441, 1929.

67. Tuft, L.: The Effect of Reticulo-Endothelial Cell Blockade upon Antibody Formation in Rabbits, J. Immunol. **27**:63, 1934.

68. Abernethy, T. J., and Avery, O. T.: Occurrence During Acute Infections of Protein Not Normally Present in the Blood: Distribution of Reactive Protein in Patients' Sera and Effect of Calcium on Flocculation Reaction with the C Polysaccharide of Pneumococci, J. Exper. Med. **73**:173, 1941.

HERPES ZOSTER APPEARING AFTER TRAUMA

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HERPES zoster appearing after peripheral nerve injury has been frequently reported in the European literature, although there are but few reports in the English literature. Such occurrence is of importance in view of laws governing workmen's compensation. Of added interest is consideration of many untoward effects of trauma and possibly, also, of factors concerned in the awakening of viruses from a condition of dormancy.

In 1947 [1] I reported eight cases of herpes zoster appearing after peripheral nerve injury, secondary to trauma of the skin or cornea. These cases conformed with the report of others in relation to the following circumstances. Herpes zoster with few exceptions affected the nerve supplying the region injured. Injury to the surface of the skin or cornea was inflicted in various ways and was of variable degree, as exemplified by the following sources: stroke of a whip, splinter of wood, splash of an irritant solution, burn, superficial laceration, or foreign body in the cornea. At times the injury is trivial, such as a slight bump of the forehead or other impact against the skin, the latter remaining intact. At times symptoms of sensory disturbance intervened between injury and the outbreak of herpes zoster. In my cases and in cases reported by others an interval of about one day to about three weeks from the time of injury to the appearance of herpes zoster predominated. It is difficult to exclude an interval of one or a few days, since in some cases there was a connecting link of subjective symptoms of nerve involvement in the interval between injury and an eruption of herpes zoster. From this pragmatic evidence we may conclude that the longer the interval beyond three weeks, the greater is the probability of a noncausal role of trauma.

Herpes zoster has also been observed to occur after intramuscular injections in the buttocks, lumbar puncture, osteopathic manipulation of the spine, and from deep roentgen therapy in the region of a ganglion.

After publication of my paper physicians wrote citing instances observed by them of herpes zoster following trauma. The following are excerpts from two such letters.

My 74-yr.-old mother had two rudimentary teeth in her left lower jaw with fistula formation. The two teeth were removed with great difficulty requiring extensive use of hammer and chisel. Exactly three weeks later, she developed herpes zoster of the first ramus of the fifth

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1. Klauder, J. V.: Herpes Zoster Appearing After Trauma, J. A. M. A. **134**:245 (May 17) 1947.

nerve on the left side, involving the cornea and causing a secondary glaucoma. Although the trauma was in the region of the third ramus, I still feel, after reading your article, that it might have been the cause of the herpes.

On Sept. 7, I sat heavily into a wingback chair without noticing that the corner of the radiator protruded into the chair. This corner gave me a padded blow into the left lower ribs.

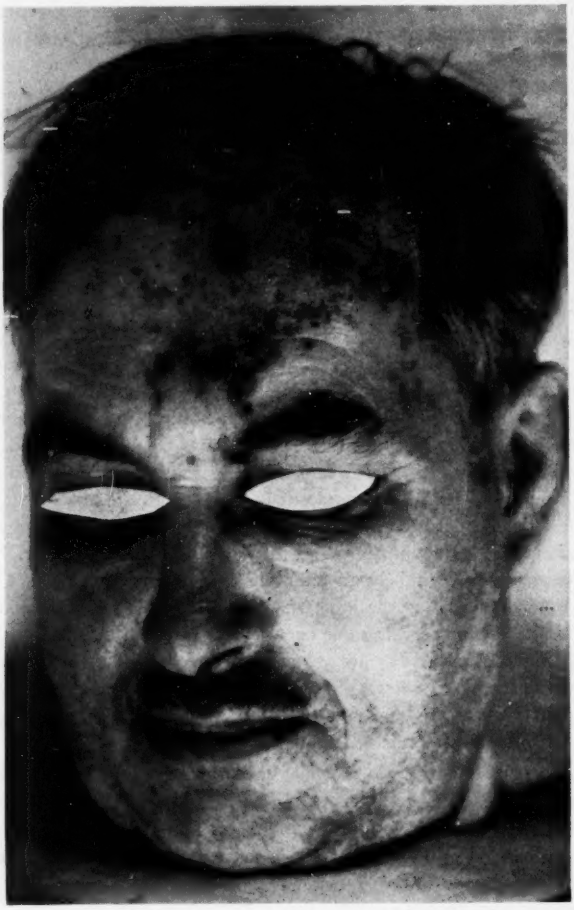

Fig. 1.—Eruption of herpes zoster on left side of scalp and forehead which appeared 30 hr. after a metal chip caused abrasion on upper part of forehead just to left of midline.

Sept. 10, I had pain in the area; there was no bruise. Sept. 12, I just noticed an area of hypaesthesia anteriorly below the left nipple. Sept. 15, came the first herpetic lesion right where the radiator hit me. Later other lesions came, centering along the course of the nerve.

I have observed the following nine additional cases of herpes zoster appearing after trauma.

REPORT OF CASES

CASE 1.—Two days after the patient received an injection of liver extract in the arm, radiating pain appeared in the same arm, followed in two more days by an outbreak of herpes zoster.

CASE 2.—An osteopathic manipulation of the spine was given the patient on Wednesday and again on Friday. On the following Sunday an eruption of herpes zoster appeared over the right buttock.

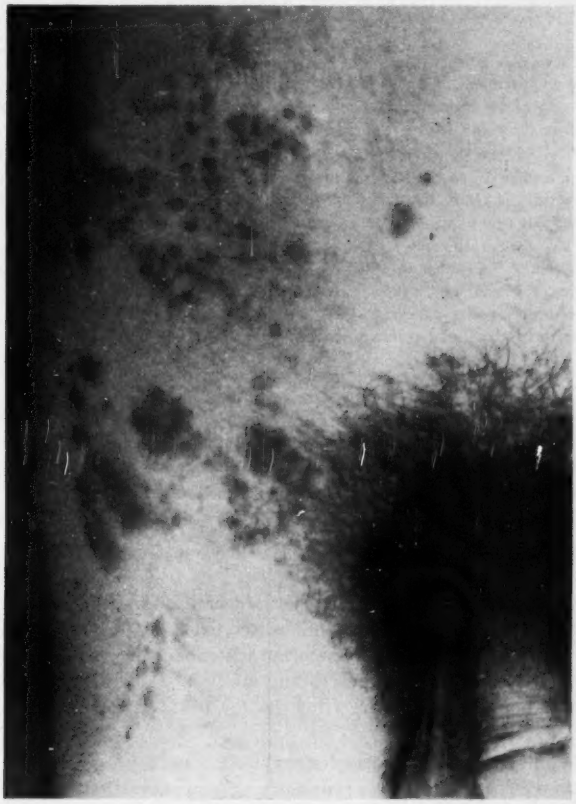

Fig. 2.—Eruption of herpes zoster which appeared 30 hr. after patient slipped, striking left knee and forcibly abducting right leg.

CASE 3.—When walking down a steep path, the patient slipped, striking the right side of the chest against a rock. He did not fall to the ground, and the skin at the site of injury remained intact. Three days later herpes zoster appeared on the right side of the chest.

CASE 4.—For pain in the region of the left shoulder the patient was treated by an osteopathic physician at weekly intervals by manipulation and faradic current. After the fourth treatment herpes zoster appeared. There were lesions on the left side of the upper part of the back and the left arm and forearm.

CASE 5.—The patient slipped on a mat; the left knee struck the floor. The head was not bumped but forcibly jerked to the right causing stretching of the left side of the neck. An

aching sensation on the left side of the neck persisted up to the appearance on the eighth day of herpes zoster on the left side of the scalp and forehead.

CASE 6.—A worker was filling a hopper with steaming hot mincemeat; some splashed on the forehead above the left eyebrow. It was wiped away, and she continued to work. The next day a blister appeared at the site of the injury with surrounding marginated redness and swelling. The appearance was not that of a first degree burn. The lesion remained solitary and disappeared with scar formation. There was no evidence of pyogenic infection. Soon after the onset of the lesion there was a sense of soreness and ache confined to the left side of the scalp and forehead. These symptoms and prompt response to aureomycin suggested herpes zoster.

CASE 7.—A worker bumped the right side of the back of his head on beef when engaged in a cold storage compartment. He was not cognizant of a laceration and continued to work. Six days later there was an outbreak of vesicles which remained confined to the region of injury. Pain, localized to the right side of scalp and neck, appeared soon thereafter.

CASE 8.—The patient shown in Figure 1 operated a machine that emitted metallic chips. About 10 a. m. a chip struck the left side of his forehead, causing a small erosion, to which he applied an ointment. Late in the afternoon of the following day an eruption of herpes zoster appeared on the left side of the forehead. The cornea was not affected.

CASE 9.—The patient shown in Figure 2 was an automobile mechanic. While lifting an engine from the floor, he slipped; the left knee struck the floor, and the right leg was forcibly abducted. He experienced pain in the region of Poupart's ligament and soreness which persisted. An eruption of herpes zoster appeared 30 hr. later. This affected the right side of the buttock extending anteriorly above and below Poupart's ligament as shown in Figure 2.

COMMENT

It becomes apparent from the foregoing case records that herpes zoster may appear not only at the site of direct injury to the skin but also in a region that has been forcibly stretched or twisted. This is exemplified by osteopathic manipulation in Cases 2 and 4, and by other circumstances in Cases 5 and 8.

In Cases 6 and 7, the vesicles of herpes zoster remained confined to the site of injury, suggesting an abortive form of herpes zoster. This was observed two times in the total series of 17 cases.

In my original report discussion was made of the following possibilities concerned in etiology. The virus of herpes zoster exists in the body at the time of injury, the latter producing a locus minoris resistentiae; the virus is introduced at the time of injury, resulting in an ascending infection of the nerve, or the nerve is involved through a transfer of the virus, by the blood stream, since the virus is neurotropic.

It is well known that herpes simplex may follow exposure to the sun or appear during fever. Herpes zoster may occur as an untoward reaction to arsenic. These occurrences evidence the influence of endogenous and exogenous factors in awakening viruses from a condition of dormancy.

Since my report other cases of herpes zoster following trauma have been reported by Borelli,[2] Selling,[3] and Epstein.[4]

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2. Borelli, D.: Herpes Zoster Following Roentgenotherapy, Ateno parmense **18**:82, 1947.

3. Selling, L.: Relationship of Trauma and Herpes: Report of 3 Cases, Portland Clin. Bull. **1**:75, 1948.

4. Epstein, L.: Herpes Zoster Following Operations for Facial Pain: Clinical Investigation on 830 Cases, Acta psychiat. et neurol. **23**:13, 1948.

GENERALIZED MILIARIA RUBRA ASSOCIATED WITH ABNORMAL VITAMIN A METABOLISM

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IN RECENT years it has been shown clinically and experimentally [1] that miliaria rubra is a phenomenon of sweat retention resulting from hyperkeratotic plugging of the orifices of the sweat glands. The patient whose case we are reporting had generalized miliaria rubra associated with anhidrosis and subnormal absorption and utilization of vitamin A.

REPORT OF A CASE

The patient was a white male physician, 64 yr. old, from Illinois, whose chief complaint was that of generalized pruritus of two-and-a-half years' duration and intolerance to heat of one-year's duration. The generalized pruritus either was more intense during hot weather or was associated with physical exertion. Roughness of the skin was noted by the patient during this time, but no eruption was observed until a year before study at the Mayo Clinic, when an urticarial, macular, and erythematous dermatosis developed first on the exposed portions of the body and gradually progressed to involve the entire body. This eruption was more pronounced

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From the Hitchcock Clinic, Dartmouth College (Dr. Lobitz) and the Section on Dermatology and Syphilology, Mayo Clinic (Dr. Kierland).

1. Sulzberger, M. B., and Emik, L. O.: Studies on Prickly Heat: I. Clinical and Statistical Findings, J. Invest. Dermat. **7**:53-59 (Feb.) 1946. Sulzberger, M. B., and Zimmerman, H. M.: Studies on Prickly Heat: II. Experimental and Histologic Findings, ibid. **7**:61-68 (Feb.) 1946. Sulzberger, M. B.; Zimmerman, H. M., and Emerson, K., Jr.: Tropical Anidrotic Asthenia (Thermogenic Anhidrosis) and Its Relationship to Prickly Heat, ibid. **7**:153-164 (Aug.) 1946. Sulzberger, M. B.; Herrmann, F., and Zak, F. G.: Studies of Sweating: I. Preliminary Report with Particular Emphasis on a Sweat Retention Syndrome, ibid. **9**:221-242 (Nov.) 1947. Shelley, W. B.; Horvath, P. N.; Weidman, F. D., and Pillsbury, D. M.: Experimental Miliaria in Man: I. Production of Sweat Retention Anidrosis and Vesicles by Means of Iontophoresis, ibid. **11**:275-290 (Nov.) 1948. Shelley, W. B., and Horvath, P. N.: Experimental Miliaria in Man: II. Production of Sweat Retention Anidrosis and Miliaria Crystallina by Various Kinds of Injury, ibid. **14**:9-20 (Jan.) 1950; Experimental Miliaria in Man: III. Production of Miliaria Rubra (Prickly Heat), ibid. **14**:193-203 (March) 1950. Shelley, W. B.; Horvath, P. N., and Pillsbury, D. M.: Anhidrosis: An Etiologic Interpretation, Medicine, to be published. O'Brien, J. P.: A Study of Miliaria Rubra, Tropical Anhidrosis, and Anhidrotic Asthenia, Brit. J. Dermat. **59**:125-158 (April-May) 1947; Tropical Anhidrotic Asthenia: Its Definition and Relationship to Other Heat Disorders, Arch. Int. Med. **81**:799-831 (June) 1948; The Etiology of Poral Closure: An Experimental Study of Miliaria Rubra, Bullous Impetigo, and Related Diseases of the Skin, J. Invest. Dermat. **15**:95-152 (Aug.) 1950.

during warm weather. During the year the patient noted weakness, and his oral temperature would rise to approximately 101 F. Tachycardia, palpitation, urinary urgency, and incontinence would appear during these heat spells, with occasional fainting.

The routine physical examination revealed normal conditions except for generalized subsiding miliaria rubra and hypotension with blood pressure of 104 mm. of mercury systolic and 76 diastolic. Laboratory studies, including urinalysis, leucocyte and erythrocyte counts, determination of hemoglobin, differential count of leucocytes, serologic tests for syphilis, and roentgenographic examination of the chest, showed no significant abnormalities. In addition, values for sugar, urea, chlorides, and bilirubin in the blood were normal. A test of liver function revealed no retention of dye.

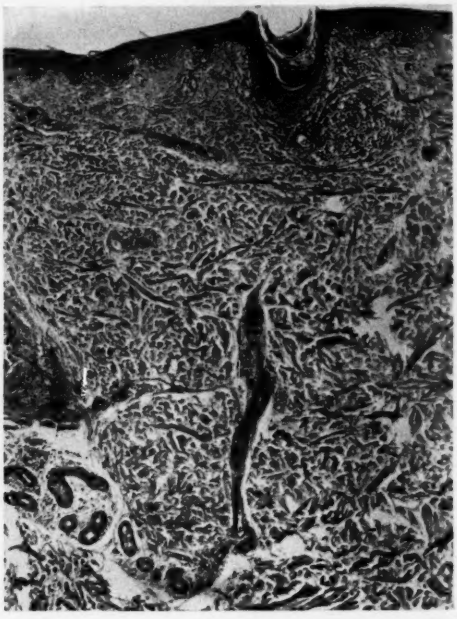

Fig. 1.—Hyperkeratosis of the eccrine sweat-duct opening with lymphocytic periductal infiltrate adjacent to the epithelial plug and also about the sweat duct as it passes through the dermis. Perivascular infiltrate is also present. (Low power, hermatoxylin and eosin; × 65.)

Microscopic examination of a specimen of skin revealed hyperkeratotic epithelial plugs in the dilated orifices of the eccrine sweat glands, with periductal lymphocytic infiltrate (Figs. 1, 2, and 3).

Because of the patient's history, further studies were done in rooms with constant temperature. The results, which are given in Table 1, showed good adjustment to temperatures below sweat-stimulating levels.

The functional capacity of the patient's sweating mechanism was investigated next, and it was found that no sweat could be demonstrated, using cobalt nitrate as an indicator, after the subcutaneous injection of 5 mg. of furtrethonium (furmethide®) iodide, nor was there any exacerbation of the miliaria. A day later the patient was exposed to a temperature of 145 F. in a heat cradle for 10 min.; at this time sweating was noted in both axillae, in a small band around the neck, on the medial surface of the right ankle, and on the dorsum of the left fourth

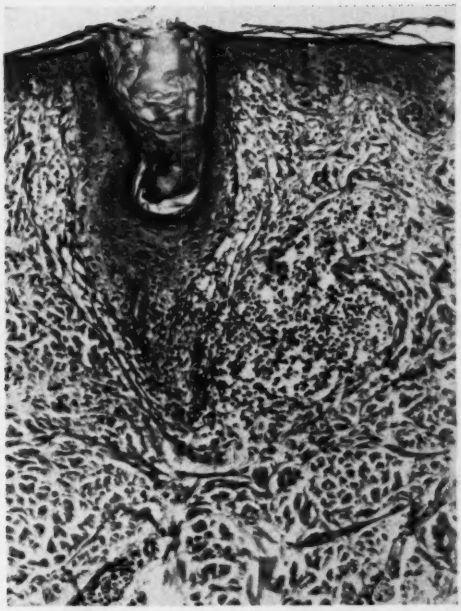

Fig. 2.—The plugged sweat duct opening and the adjacent lymphocytic infiltrate under higher power (hematoxylin and eosin; × 100).

Fig. 3.—Infiltrate about the coil portion of the sweat gland (hematoxylin and eosin; × 100).

toe. There was complete suppression of sweat elsewhere. The oral temperature at the end of the exposure to heat was 100.8 F. Generalized miliaria rubra developed rapidly while the patient was subjected to this heat test.

Multiple determinations of the blood pressure were done before and after the exposure to heat because of the history of a status approaching shock. The findings (Table 2) indicate the duplication of the previous episodes.

TABLE 1.—*Skin Temperatures in Degrees Centigrade*

Constant-Temperature, Room	Air	Right First Toe	Left First Toe	Right Third Toe	Left Third Toe	Right First Finger	Left First Finger	Right Third Finger	Left Third Finger
Normal temperature	26.3	27.3	27.1	27.2	27.5	35.0	35.8	34.7	34.2
Hot room	28.7	28.9	28.2	28.5	28.2	35.7	35.8	34.7	34.3

TABLE 2.—*Blood Pressure and Pulse Rate Before and After Exposure to Heat*

Time	Blood Pressure, Mm. of Hg	Pulse per Minute
Before heat, standing	116/80	100
	104/56	96
	108/56	92
After heat, standing		
30 seconds	90/50	100
1 min	98/56	96
2 min	94/54	100
3 min	100/54	100
4 min	96/58	104
5 min	88/56	100
6 min	88/52	102
7 min	90/58	100
8 min	88/56	104
9 min	86/58	100
10 min	80/50, lightheaded	104
11 min	Fainted	...

TABLE 3.—*Results of Vitamin-A-Tolerance Test*

Time	Quantity in 100 Cc. of Plasma: Carotene, I. U.	Quantity in 100 Cc. of Plasma: Vitamin A, I. U.
First test		
Fasting	171	117
5 hr.	168	371
24 hr.	163	357
Seven months after first test		
Fasting	154	295
5 hr.	163	784
24 hr.	163	464

Since the relationship of excess keratinization of the epidermis to abnormal metabolism of vitamin A has been etiologically stressed in a number of cutaneous diseases, the patient's status was investigated in this regard. The tests of visual dark adaptation [2] exhibited abnormally high

2. Brunsting, L. A., and Sheard, C.: Dark Adaptation in Pityriasis Rubra Pilaris, Arch. Dermat. & Syph. **43**:42-61 (Jan.) 1941. Sheard, C.: Courses of Dark Adaptation and Levels of Vitamin A and Carotene in Normal and Clinical Conditions, Federation Proc. **7**:113-114 (March) 1948.

pathologic readings, while the vitamin-A-tolerance test [3] indicated a subnormal absorption or utilization of vitamin A (Table 3).

Accordingly, the patient was given vitamin A, 200,000 units by mouth daily, and Burbot liver oil, 40,000 units twice weekly, intramuscularly. He was instructed also to apply a salicylated alcohol solution to his skin once or twice daily.

Seven months later the patient returned for further observation. He had continued treatment except that he had discontinued the intramuscular doses of vitamin A because of local discomfort. The miliaria rubra had subsided, but the anhidrosis and intolerance to heat had persisted. On exposure to heat his oral temperature would rise to 102 F., but he had only "fainted" once, when in New Orleans. He obtained relief by immersing himself in a cold bath for half an hour.

On this visit results of the general examination were again essentially normal except for low blood pressure of 110 mm. systolic and 72 diastolic. At this time the vitamin-A-tolerance test showed but slight improvement as a result of oral administration of vitamin A (Table 3).

The patient was advised to continue to take the vitamin A by mouth. This he had done during the intervening years since his last visit in 1947. He has reported, however, that he has become steadily worse: The intolerance to heat is more pronounced, the pruritus is severe, and sweating has not returned. He has been forced to give up his practice and move to a more equable climate, but this has not proved beneficial.

COMMENT

Anhidrosis, whether partial or complete, may be due to a number of factors, including obstruction of the sweat duct as in miliaria rubra or tropical anhidrotic asthenia. It may be produced by anatomic abnormalities, loss in number or lack of development of the sweat glands, as in ectodermal defects, or by a defect of innervation as in the anhidrosis following sympathectomy. We were unable to demonstrate any reason for the anhidrosis in this case except the obstruction of the duct. The number and anatomy of the coil glands and ducts seemed normal in the microscopic sections, and there was no evidence of neurologic disease or abnormality. Until the advent of the miliaria two and one-half years prior to coming under our care, the patient had sweated normally. It is possible that the chronic unrelieved obstruction at the mouth of the coil duct, with its attendant inflammatory reaction, has produced functional atrophy of the coil gland itself. This could not be demonstrated at biopsy at the first visit, but it is conceivable that such could be demonstrated now, four years later.

In the conditions in which lack of absorption or utilization of vitamin A has been incriminated etiologically, administration of vitamin A therapeutically either by mouth or parenterally has not given completely satisfactory results, nor does the result of the vitamin-A-tolerance test give complete information. Because of this, we are unable to state with complete certainty that a metabolic fault of vitamin A played a great role in the production of this syndrome. Nevertheless, the findings indicate that the miliaria was improved when vitamin A was first given and that the vitamin-A-tolerance test and visual dark-adaptation test revealed subnormal conditions.

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3. Ruch, D. M.; Brunsting, L. A., and Osterberg, A. E.: Use of Vitamin A Tolerance Test in Certain Cases of Dermatologic Disorders, Proc. Staff Meet., Mayo Clin. **21**:209-217 (May 29) 1946.

The patient had mild hypotension, yet not true orthostatic or even postural hypotension. The decreasing blood pressure after exposure to heat is probably a secondary, rather than a primary, factor and related to the fever and anhidrosis from which the episodes of fainting develop. This same group of symptoms may be found in patients who have complete, or almost complete, anhidrosis from other causes.

SUMMARY

A patient with generalized miliaria rubra and anhidrosis has been found to have subnormal absorption or utilization of vitamin A as indicated by a "flat" vitamin-A-tolerance curve and a delay in visual adaptation to darkness. Except for mild hypotension, no other significant abnormalities could be demonstrated.

EARLY DERMATOLOGIC ILLUSTRATION

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NO BRANCH of medicine lends itself so well as dermatology to the use of visual-education aids. Very early in the history of the specialty the need was felt for graphic representation to accompany the authoritative treatises, and it is not too much to say that the modern phase of dermatology began with successful methods of illustration. In this photographic age one tends to forget that the camera is not the only, nor even always the best, means of recording skin disease. My purpose is to review the early collections of engravings and lithographs which our predecessors found to be of greatest value in stabilizing the nosology of the specialty in its formative days.

Although occasional isolated woodcuts representing skin disease, particularly syphilis, have existed for centuries,[1] the first systematic grouping of illustrations and descriptions of disease was accomplished by the great English physician Robert Willan (1757-1812). As early as 1784 Willan had formulated a classification of skin diseases based on the morphology of the essential lesion, modified from the work of von Plenck (1738-1807), and consisting of eight orders: papulae, squamae, exanthemata, bullae, vesiculae, pustulae, tubercula, and maculae. By 1786 he had begun to include sketches of the eruptions, with descriptions of those which he considered to be classic types.[2] Later, as this practice became standard with him, his sketches became more elaborate, many of them being engraved on copper.

A grand project took shape in his mind, a comprehensive and completely illustrated dermatologic text. From 1796 to 1808 he published in four parts his "On Cutaneous Diseases," [3] which, according to Bloch, "had the greatest recognition in all European countries such as no other treatise on the subject before or since has received." [4] Published with the text, for the first time in dermatologic

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1. Examples of early woodcuts may be found as title pages in the following publications: Steber, B.: A Malafranczos, morbo Gallorum, Vienna, 1498; Grunpeck: Tractatus de pestilentiale, Augsburg, 1496; Blankaart: Venus belegert en Ontset, Amsterdam, 1684.

2. Bateman, T.: Biographical Memoir of the Late Dr. Willan, Elinburgh M. & Surg. J. **8**:502, 1812.

3. Willan, R.: On Cutaneous Diseases, London, 1808.

4. Bloch, I., cited by Lane, J. E.: Robert Willan, Arch. Dermat. & Syph. **13**:737 (June) 1926.

history, were 30 hand-colored prints. Willan's evaluation of this new approach seems quite modern in its perspective [5]:

> In order to convey distinct ideas on the subject, I shall elucidate every genus by coloured engravings representing some of its most striking varieties. This method is new and will be attended with many advantages; though at the same time subject to a variety of imperfections. Such representations cannot sufficiently express the various degrees of opacity and clearness in Pustules; nor the quantity or quality of the matter discharged from superficial ulceration: neither can they extend to every minute circumstance in the course of the disease, being necessarily taken at some fixed period of it. I would therefore wish the drawings to be considered only as auxiliaries to the verbal descriptions: as such, they will be more especially useful in shewing the number, form, size, and colour of the Papulae, Pustules, Tubercles, Spots, etc. constituting the disease, which appearances cannot always be communicated in words.

The plates were engraved from drawings by Edwards, Strutt, Perry, Kirkland, Darton, and Cruickshank. Willan himself prepared several of the drawings in their final form, and it is not certain whether he had these artists work from life or from his collected sketches. At any rate, most of the figures are poorly drafted. The engraving is clear and simple. In this matter, Willian was difficult to satisfy, and he often required that plates showing even minor flaws be discarded. Yet the prints show nothing like the technical skill to be found in the work of contemporary artistic engravers. Despite these drawbacks, there is in the collection a certain redeeming clearness of purpose, and through it Willan was, in general, successful in showing what he intended.

The illustrations for "On Cutaneous Diseases" were representations of only the first four orders of the Willan system. The originator died before he could complete his work. His brilliant pupil, Thomas Bateman (1778-1821), bought up the copyrights and came into possession of the unpublished sketches in Willan's portfolio. Bateman finished the engraving of these, added a few originals, and combined them with the plates of the original publication, "improved at considerable expense by the able hands of Mr. Stewart." The whole was published from 1814 to 1817 as an atlas entitled "Delineation of Cutaneous Diseases Exhibiting the Characteristic Appearances of the Principle Genera and Species Comprised in the Classification of the late Dr. Willan." [6]

It is interesting that Bateman omitted Dr. Willan's sketches of syphilis. He stated, "It would be presumptuous, in the present state of our knowledge, to determine the eruptions of true Syphilis." [7]

There can be no doubt that Stewart's were able hands, for his original engravings are superior to any of those previously published, and the older plates which he improved have a brighter appearance, despite the fact that by this time they must have worn considerably (Fig. 1). Tinting is better handled in this edition.

Bateman performed his task in the spirit of his master, and the general effect and usefulness of this first true atlas are the same as the original group of illustrations from which it grew.

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5. Willan,[3] Introduction, p. viii.

6. Bateman, T.: Delineations of Cutaneous Diseases, Exhibiting the Characteristic Appearances of the Principle Genera and Species Comprised in the Classification of the late Dr. Willan, London, 1817.

7. Bateman,[6] Preface, p. vi.

Jean Louis Alibert (1766-1837) was the founder of the French School of dermatology. Drawing on his vast experience at L'Hôpital Saint Louis in Paris, he formulated a "natural," or Linnean-type, classification for skin diseases, which he spent the rest of his life perfecting and advertising.[8] He erected a "tree of dermatoses" with 12 main branches and many subdivisions, the pictorial representation of which forms the frontispiece for all of his later works. Oliver Wendell Holmes recalls him as "jolly old Baron Alibert whom I remember so well in his broad brimmed hat, worn a little jauntily to one side, calling out to the students in the County and of L'Hôpital Saint Louis 'Ènfans de la méthode naturelle, êtes

Fig. 1.—Sycosis menti (Sycosis barbae), from the Willan and Bateman atlas.

vous tous ici.'"[8] The classification did not survive him, being discarded as too cumbersome even by his foremost pupil, Laurent Biett (1781-1840).[9]

In 1806, before the publication of the final fasiculus of Willan's "On Cutaneous Diseases," Alibert brought out his "Description des maladies de la peau."[10] This was the first of his works detailing the "méthode naturelle," and he included with it 53 hand-colored engravings illustrating the branches of his tree. Although Alibert

8. Garrison, F. H.: Introduction to the History of Medicine, Philadelphia, W. B. Saunders Company, 1929, p. 417.

9. Garrison, F. H.: Introduction of the History of Medicine, W. B. Saunders Company, 1929, p. 418.

10. Alibert, J.-L.: Description des maladies de la peau observées à l'hôpital Saint-Louis, Paris, 1806.

was familiar with Willan's "artificial" classification, it is doubtful whether he knew of his plates, for he regarded himself as the first to use illustrative methods.

He laid out his purposes in his most characteristic manner in the preliminary section of the work mentioned above [11]:

To stamp the seal of authenticity on that which I have written, to add to the energy and power of my discourse, to perpetuate and animate in some way all of my descriptions, I have considered it my duty to have recourse to the ingenious artifice of the brush and the burin. I have attempted to strengthen the impressions of the pathologist; I have attempted, finally, by the striking colours of the painter, to instruct, as it were, the sight through seeing, to show off and to contrast in a better manner the characteristics of the diseases of the skin, to establish their finer

Fig. 2.—Scrophule endémiqe (endemic cretin), from the Alibert plates.

hues, to reach in a word the understanding of my readers, and to reproduce living before them the various phenomena that have amazed these eyes.

The plates in this work are truly superb, far excelling in draftmanship, clarity, and detail those of Willan and Bateman. However, the cases selected for portrayal are often in a state far advanced, or are extremely bizarre, chosen more with the Alibertian sense of showmanship than with regard to "strengthening the impressions of the pathologist," and, in keeping with the author's feelings, less attention is given to the elementary lesions. Working wholly in the spirit of things, the artist displays a fine sense of distortion for effect, even almost of caricature, reaching his peak in a fascinating portrait of an endemic cretin (Fig. 2). This approach, however,

11. Alibert,[10] Preliminaire, p. xxi

limits the usefulness of the figures for the practicing physician, and in this respect the more prosaic plates of Willan and Bateman were undoubtedly superior.

The name Moreau Valvile appears on many of the plates, and others are certainly his work. Nothing is known of him.

A second edition, thoroughly revised, was published in 1833.[12] This contained the definitive exposition of the "nosologie naturelle," complete with the tree frontispiece, in full color now, with a flamboyant orange and green serpent supporting the title scroll. A few new plates were added, colors brightened, and labels changed to conform with the expanding classification.

In keeping with Alibert's personality, both these atlases were printed on huge formats, about 14 by 22 in. (36 by 56 cm.), and, what with copper-plate engraving of such fine quality, must have been enormously expensive.

Alibert's varied repertoire of pontification, verbosity, huckstering, and general megalomania annoyed his more reserved English colleagues. Prevalent opinion found its most effective spokesman in Bateman[13]:

> M. Alibert, with loud pretensions to superior skill, and much vaunting of the services which he has rendered this department of medicine has, in fact, contributed nothing to the elucidation of the obscurity in which it is veiled. The merit of his publication belongs principally to the artists whom he has had the good fortune to employ.

Pierre François Rayer (1793-1867) (with Cazenave and Biett) succeeded Alibert to authority in France. His "Traité théorique et pratique des maladies de la peau" (1827) was extremely influential both at home and abroad, particularly in England, where several independent translations were made of the work. He admired Willan, affirmed the accuracy of the latter's observations, and retained his vocabulary: "One cannot help acknowledging that Willan is, of all who have written of diseases of the skin, the one whose descriptions are most constantly correct."[14]

Rayer had some qualms about attempting to illustrate his "Traité" and needed help[15]:

> But the difficulties in the execution of such an enterprise would have dissuaded me, if the devoted friendship of M. James Young, of Paisley, who combines a profound understanding of skin diseases with the talent for perceiving wonderfully their appearances and of representing them with great fidelity, had not come to my rescue.

Young worked with a M. Prêtre in the design of the plates, and Forrester and Langlois engraved them. They numbered 22 in all, with over 400 figures. There is nothing pretentious here, simple engraving, typical cases, straightforward presentation (Fig. 3). Unfortunate crowding of the plates and inferior tinting detract from an otherwise workmanlike, useful job. The collection was published in 1827 as an atlas bound separately from the work it was designed to illustrate, and ran through several editions.

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12. Alibert, J.-L.: Clinique de l'hôpital Saint-Louis, Paris, 1833.

13. Bateman, T.: A Practical Synopsis of Cutaneous Diseases, ed. 3, London, 1814, Preface, p. xii.

14. Rayer, P. F.: Traité théorique et pratique des maladies de la peau, Paris, 1826-1827, Preface.

15. Rayer, P. F.: Atlas to Traité théorique et pratique des maladies de la peau, ed. 2, Paris, 1835, Préface, p. 6.

Robert Willis (1798-1878) was not a dermatologist of the specialized variety that already existed in his day. Neither was he any ordinary physician, his interests being extremely discursive and embracing many fields of literature and science. In his position as librarian of the English Royal College of Surgeons he had become

Fig. 3.—Plate on alterations of the papillae, epidermis, nails, and hair, from the Rayer atlas.

familiar with the confusion existing in the identification and classification of dermatologic disease. His interest in these diseases had further been stimulated through his translation into English of Rayer's work on the subject.[16] He himself had

16. Obituary, Brit. Med. J. **11**:498, 1878. Obituary, Medical Times & Gazette **2**:422, 1878.

acted as ghost writer for a book on dermatologic therapy, and when it was favorably noticed by the press, he, as the *Lancet* put it, "imprudently avowed himself the author, which lost him not only the friendship of the person alluded to, but also the commission to write another book on the same subject." [17]

Willis was also an admirer of Willan. He felt that the older man's purpose had not been appreciated properly by his successors, that the purpose was "to render an account of the nature, symptoms, and diagnostic marks of the disease generally of which his figure was the individual expression, and to apply the knowledge thus acquired to its legitimate end, the alleviation or cure of the malady." [18] This Willis proposed, by his publication, to do himself.

Further, in planning an atlas, he outlined the object of every iconographic work as "the union of pictorial representation with practical knowledge at moderate expense." [18b]

In his intellectual excursions he had become familiar with Aloys Senefelder's lithographic process which, although it had been known in England since 1801, had only recently aroused real interest.[19] In this method of reproduction he found the solution to the problem of expense which had so seriously limited the usefulness of all previous worthwhile works.

With this important obstacle overcome, he hired an artist to sketch from life those cases which he thought to be most instructive and proceeded to arrange the plates in the nosological fashion of Willan. From his own words on the selection of plates, a glimpse may be had of that strong personality which brought him into collision with more than one authority in his life time [18b]:

> Determined to avoid everything like crowding my plates, I have resolved rather to content myself with giving delineations of eighty or ninety subjects that shall never afterwards be confounded with one another, nor with anything else, than to produce three or four hundred among which doubt and uncertainty must of necessity have remained. In from eighty to one hundred plates, embracing the same number of subjects, I conceive that I can exhibit almost every disease that commonly occurs or that is really important.

He disliked the short descriptive headings that Bateman included with the Willan plates: "Nor could I with my views be satisfied to give a barren account, two or three lines in length, of the individual I have represented. This were but playing showman to the painter." [18b]

The accounts which Willis placed with his illustrations are models of careful descriptive writing, brief but not barren.

It is known that Willis did not do well in private practice. In discussing psoriasis he remarked, "My experience in cutaneous disease generally, enables me to say that I find patients even more intractable than their ailments."[20]

The completed version of this atlas was published in 1840 and was called "Illustrations of Cutaneous Disease, A Series of Delineations of the Affections of the Skin in Their More Interesting and Frequent Forms."[18a]

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17. Obituary, Lancet **2**:532, 1878.

18. (*a*) Willis, R.: Illustrations of Cutaneous Disease, A Series of Delineations of the Affections of the Skin in Their More Interesting and Frequent Forms, London, 1840; (*b*) ibid., advertisement.

19. Hartrick, A. S., in Chamber's Encyclopaedia, edited by M. D. Law, London, Newnes, 1950, vol. 8, Lithography.

20. Willis,[18] psoriasis inveterata.

The illustrations are fine pieces of work. We know nothing of the artist, Archibald Henning, who not only drew all the figures from life but who also transferred them to the lithographic stone himself. His figures have about them an air of spontaneity. A sense of realism is conveyed. They are totally unlike the artificial and stereotyped lithographs that became so popular in other fields. There is everywhere attention to detail without overloading and resultant obscurity (Fig. 4). The coloring in the specimens I have seen is excellent.

All these works contain errors and, in the light of present day knowledge, fail to represent accurately whole classes of cutaneous disease. None knew this better

Fig. 4.—Trichosis lupinosa (Favus), from the Willis atlas.

than Willis, who said, "We have often to sit down at last content with our efforts to succeed, rather than with our success."[21] And, although these hand-colored productions gave way to the more elaborate and cheaper works that came with the development of chromolithography in the middle of the century, they had succeeded in enabling men to visualize, for the first time, diseases which a thousand words are inadequate to describe.

5125 Baltimore Ave.

21. Willis,[19] postcript.

CYSTEINE AS LOCAL PROTECTIVE TO HUMAN SKIN AGAINST X-RAYS

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AND
THEODORE CORNBLEET, M.D.
CHICAGO

INVESTIGATORS long have sought means of protection against harm from radiation. The threat of mass injury in the atomic age accentuates all the more the urgent necessity for this research. This form of physical energy characteristically penetrates the deeper parts of the body, yet the skin by its exposed position remains the organ of primary attack. The accessibility of the skin as a target and the simplicity of retrieving it for study are advantages favoring its use for experimental purposes. The dermatologist naturally has an interest in any cutaneous study; but, because he so frequently resorts to the use of radiation therapy, he pays inordinate attention to investigations in this realm of biophysics.

The literature covering this field of activity is becoming so large as to be beyond the compass of any except the specialist. A few samplings from it may be a short-cut to the point. Knowlton, Hempelmann, and Hoffman [1] observed the effects of x-rays on the mitotic activity of mouse epidermis. They found that this activity is extraordinarily sensitive to the effects of x-rays and that the best index of damage is the time required for the mitotic index to return to normal. Griffith and his co-workers [2] demonstrated that flavonoids exert a beneficial effect in experimental roentgen-irradiation injury. They found that rutin accelerated the restorative processes following severe x-ray burns of rats' extremities. Clark and his group [3] found that a flavonoid preparation derived from lemons (vitamin P) reduces the mortality from total-body roentgen irradiation by about half. Sokoloff and his co-workers [4] corroborated these results and suggested that the increased capillary fragility induced by radiation injury may be prevented by large doses of the flavonoids naturally present in citrus fruit.

From the Departments of Dermatology, University of Illinois College of Medicine (Dr. F. E. Senear, Chief), and the Cook County Hospital.

1. Knowlton, N. P., Jr.; Hempelmann, L. H., and Hoffman, J. G.: The Effects of X-Rays on the Mitotic Activity of Mouse Epidermis, Science **107**:625, 1948.

2. Griffith, J. Q., Jr.: Rutin: Therapy for Hemorrhagic Complications of Hypertension (William Hamlin Wilder Memorial Lecture), Proc. Inst. Med. Chicago **16**:434, 1947. Griffith, J. Q., Jr.; Anthony, E.; Pendergrass, E. P., and Perryman, R.: Production of Increased Capillary Fragility in Rats Following Irradiation, Proc. Soc. Exper. Biol. & Med. **64**:332, 1947.

3. Clark, W. G.; Uncapher, R. P., and Jordan, M. L.: Effect of Flavonoids (Vitamin P) on Mortality from Total Body Roentgen Irradiation, Science **108**:629, 1948.

4. Sokoloff, V.; Redd, J. B., and Dutcher, R.: Vitamin P Protection Against Radiation, Science **112**:112, 1950.

Barron [5] found that sulfhydryl-containing enzymes are readily oxidized by radiation and that it is possible to reactivate such enzymes after moderate radiation doses upon addition of a reducing agent, such as the sulfhydryl-containing glutathione. Patt and his associates [6] found that cysteine, a sulfhydryl-containing amino acid, injected intravenously into rats could appreciably protect them from the effect of irradiation of the whole body. Forssberg,[7] using cysteine, too, gave protection to bacterial cells if he gave cysteine to them immediately before irradiation. He found that other SH-containing chemicals act similarly, but that related compounds that do not contain a sulfhydryl compound offer no protection. In addition, he believes that he showed that cysteine injected in proper doses into the skin of guinea pigs more or less prevents roentgen epilation.

Because of this suggestive evidence of the protective effects of SH-group-containing materials, we decided to make observations on the action of cysteine when injected into the human skin. We used a freshly prepared solution of cysteine hydrochloride in a buffer solution (sodium phosphate 0.125M-pH 7.2), 1.5 gm. to 100 cc. We injected this solution into the left scapular area so as to make a wheal 2 cm. in diameter. A wheal of buffer solution alone at the midline of the back and the bare skin itself of the right scapula served as control areas. We used a lead

Results of Experiment

Patient	H. J.	F. E.	S. M.	B. U.
Age	15	39	65	60
Sex	M	F	F	F
Right scapular area, control	+	+	+	+
Left scapular area, cysteine	++	++	++	+++
Middle area, buffer	++	++	++	+++

sheet with an aperture of 2 by 1.5 cm. for a shield. Each site received 450 r (in air), the factors being 70 kv., 5 ma., 25 cm. distance, and a half-layer-value of 0.6 Al.

COMMENT

We found that cysteine under the terms of our experiment was unable to prevent the formation of an erythema. Perhaps the size of our x-ray dosage was too great for us to observe merely moderate effects. We felt it was necessary with our apparatus to use at least 450 r to produce appreciable changes in our subjects, because some of them showed no erythema or pigmentation whatever at the end of a week with only 400 r.

Our negative results may be due to the possibility that the protective action of cysteine and other SH-containing agents exerts itself only systemically and not locally, and we used the cysteine here only as a local screen.

5. Barron, E. S. G.: Some Aspects of the Biological Action of Radiation, Declassified Document 484, United States Atomic Energy Commission, Technical Information Division, Oak Ridge, Tenn., 1946. Barron, E. S. G.; Dickman, S.; Muntz, J. A., and Singer, T. P.: Studies on Mechanism of Action of Ionizing Radiations: I. Inhibition of Enzymes by X-Rays, J. Gen. Physiol. **32**:537, 1949.

6. Patt, H. M.; Tyree, E. B.; Straube, R. L., and Smith, D. E.: Cysteine Protection Against X Irradiation, Science **110**:213, 1949.

7. Forssberg, A.: On the Possibility of Protection the Living Organism Against Roentgen Rays by Chemical Means, Acta radiol. **33**:296, 1950.

The discrepancy in our results when compared with that of others may represent a species difference only: We employed humans, whereas they used bacteria and laboratory animals. One of us (T. C.) [8] showed such a difference in the way hair and epidermal growth responds to local applications of adrenal cortical extracts in humans in contrast to what was reported for a laboratory animal.

SUMMARY

We injected solutions of the sulfhydryl-containing amino acid, cysteine, into human skin and made observations on their protective effects against radiation. We found, in contrast to others, that under our experimental conditions, cysteine offered no protection to human skin when used as a preventative against x-radiation injury.

2 N. Sheridan Rd.

1819 W. Polk St. (12).

8. Grant, R.; Cornbleet, T., and Grossman, M. I.: Influence of Local Application of Adrenal Cortical Extract on Hair Growth in the Human, Arch. Dermat. & Syph. **62**:717 (Nov.) 1950.

RESULTS OF TREATMENT OF ACNE VULGARIS BY INTRAMUSCULAR INJECTIONS OF VITAMIN A

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SINCE Straumfjord [1] reported that the daily administration of 100,000 I. U. of vitamin A for periods of nine to 18 mo. resulted in the disappearance or the improvement of the lesions in all but three of 100 cases of acne vulgaris, vitamin A has occupied a prominent place in the treatment of that disease. Saunders [2] found that 100,000 units of vitamin A taken daily for chronic sinusitis cleared the acne vulgaris on his back in six months. Recurrence was noted after four months when vitamin A was stopped. The vitamin therapy was started again, and in three months the back was clear once more. Obermayer and Frost [3] were less enthusiastic but stated that

> vitamin A therapy is undoubtedly of benefit in the handling of some forms of acne vulgaris while others do not seem influenced by it. It seems that acne which is characterized by prominent follicular plugging in addition to the formation of comedos responds most readily to this form of treatment.

Lynch and Cook [4] gave 100,000 units of vitamin A daily to 45 university students with acne vulgaris for an average of four to five months. In 46% of the cases results could be classed as good, though in only one case was the acne apparently cured. In 27% the eruption was slightly improved, and in the remaining 27% it was unchanged.

Combes, Saperstein, and Distelheim [5] administered 100,000 units of vitamin A daily to 36 patients with acne vulgaris. Of these, 29 improved, while none experienced an exacerbation. The comedo type improved most rapidly, and the most beneficial results were observed after three months of therapy.

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1. Straumfjord, J. V.: Vitamin A: Its Effect on Acne, Northwest Med. **42**:219-225 (Aug.) 1943.

2. Saunders, T. S.: Favorable Effects of Vitamin A in a Case of Acne of Long Duration, Arch. Dermat. & Syph. **50**:199 (Sept.) 1944.

3. Obermayer, M. E., and Frost, K.: Some Phases of Vitamin Therapy in Dermatology, Arch. Dermat. & Syph. **51**:309-312 (May) 1945.

4. Lynch, F. W., and Cook, C. D.: Acne Vulgaris Treated with Vitamin A, Arch. Dermat. & Syph. **55**:355-357 (March) 1947.

5. Combes, F. C.; Saperstein, R. B., and Distelheim, I.: Vitamin A in Acne Vulgaris, M. Times, New York **77**:473-475 (Oct.) 1949.

Sulzberger and Baer [6] believe that large doses of vitamin A, 150,000 to 200,000 units daily, have a definite place in the treatment of acne vulgaris, particularly those forms which are associated with widespread horny plugging of the follicular openings. They believe that vitamin A should be employed for at least four to six months before it is given up as ineffective, as in some of their cases the disease appeared to respond only after such prolonged administration.

Savitt and Obermayer [7] state that some patients with acne vulgaris are benefited by vitamin A but that results of treatment are too unpredictable to warrant general use of such therapy at present. They were able to follow for eight months a group of 35 students each of whom received 100,000 units of vitamin A daily. Twenty of the treated group improved, 12 were unchanged, and 3 got worse.

All the authors mentioned above used an oily solution of vitamin A and have repeatedly emphasized the fact that at least three months of treatment is necessary in order to see definite improvement.

Having found that absorption, as measured by change in blood-serum concentration, was far better with vitamin A in aqueous medium than with vitamin A in oily medium, Davidson and Sobel [8] administered 36,000 to 40,000 U. S. P. units in aqueous dispersion daily for two to five months to 20 patients with acne vulgaris. There was a definite improvement in all but two in two to four weeks. At the end of therapy, seven were practically cleared or much improved, nine considerably improved, two completely cleared, and two unimproved.

In an attempt to evaluate the role of vitamin A in the treatment of acne vulgaris, 30 adolescents with this condition were selected from the patients at the Pennhurst State School for the feebleminded. Boys and girls were equally represented, and the acne vulgaris ranged in severity from comedo and papules to papules, pustules, and cysts. Information was not available as to the duration of the disease. In no instance had either local or systemic treatment been given within six months, nor were any local, dietary, or special hygenic measures undertaken. All patients were photographed two days before and one week after the course of treatment. Judgments as to change in the acne was based on a comparison of the photographs with the patients.

Because of possible individual differences in the amount and rate of absorption of vitamin A from the intestinal tract and because oral medication might be refused or forgotten by patients of this type, it was decided to administer the vitamin A parenterally. A plan calling for the administration of 100,000 U. S. P. units of vitamin A intragluteally three times a week to a total of 2,000,000 units in six and two-thirds weeks was chosen arbitrarily. It was felt that patients outside an institution would fail to persist in treatment of this type if improvement was not noted after 20 injections.

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6. Sulzberger, M. B., and Baer, R. L.: The 1947 Year Book of Dermatology and Syphilology, p. 83; The 1949 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1950, p. 14.

7. Savitt, L. E., and Obermayer, M. E.: Treatment of Acne Vulgaris and Senile Keratoses with Vitamin A: Results of a Clinical Experiment, J. Invest. Dermat. **14**:283-289 (April) 1950.

8. Davidson, D. M., and Sobel, A. E.: Aqueous Vitamin A in Acne Vulgaris, J. Invest. Dermat. **12**:221-228 (April) 1949.

Five boys and five girls were given treatment with 100,000 units of water-soluble vitamin A [9] intragluteally three times a week. To a similar group of patients was given vitamin A in oil in doses equal to those described above, while a third group of 10 children was used as a control and given no vitamin A. Nine of the group receiving the oily preparation were able to complete the course of treatment uneventfully. In one girl virus pneumonia developed in the first week of treatment, and she was relegated to the control group. The patients receiving water-soluble vitamin A were less fortunate. After the 10th injection, extremely swollen, hot, painful buttocks accompanied by fever developed in one boy, necessitating a reduction in dose to 50,000 units three times a week for the last 10 injections. One boy and one girl received only 18 injections because of painful buttocks. Discomfort in the buttocks of sufficient degree to discourage most patients was noted in practically all patients receiving the aqueous preparation.

At the completion of the course of therapy the status of the patient's acne vulgaris was compared with that in the photograph taken prior to treatment. Two physicians, in addition to us, joined in the evaluation of the results, which are summarized in the Table. It will be noted that patients receiving water-soluble vitamin A fared about as well as the controls, but those receiving the oily preparation actually did worse.

Results of Treatment of Acne by Intramuscular Injections of Vitamin A

Type of Treatment	No. Who Were Better	No. Who Were Worse	No. Who Were the Same
Vitamin A in oil	2	4	3
Vitamin A in water	1	1	8
None (control patients)	2	2	7

In only two of the 30 patients did any marked change occur. The girl in whom virus pneumonia developed after administration of 300,000 units of vitamin A in oil had no active lesions at six and two-thirds weeks, but acne recurred about a month later after her fever subsided. In one girl with papulopustular acne vulgaris, many cystic lesions developed while she was receiving vitamin A in oil. The boy in whom the dose had to be reduced showed slight improvement on 100,000 units of water-soluble vitamin A three times a week but relapsed promptly to his former condition on the smaller dosage.

CONCLUSIONS

Vitamin A in either aqueous or oily vehicle administered in doses of 100,000 units intragluteally three times a week to a total of 2,000,000 units is of no value in the management of acne vulgaris. The administration of the aqueous preparation is accompanied by much pain and often by hot, swollen, tender buttocks. In our small series of cases, patients receiving vitamin A in oil fared worse than those in our control series who received no vitamin A.

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9. The vitamin A preparations used in this experiment were purchased in the open market. The aqueous product employed was "aquasol" A, U. S. Vitamin Corporation, each 2.0 cc. ampule containing 50,000 U. S. P. units vitamin A. The oily preparation used was "A-vita," The Vitarine Company, Inc., supplied in 30 cc. ampule vials, each cubic centimeter containing 100,000 U. S. P. units of vitamin A in sesame oil.

EFFECTIVE APPLICATION OF BANTHINE® IN DERMATOLOGY

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GRIMSON and his co-workers recently advocated in a preliminary report of four cases the successful use of a new anticholinergic drug, banthine® bromide (beta-diethylaminoethyl xanthene-9-carboxylate methobromide), in the treatment of hyperhidrosis.[1] The purpose of this report is to describe the use of banthine® bromide not only in the treatment of hyperhidrosis but also in the treatment of several of the common dermatoses aggravated by or possibly produced by excessive sweating.

Twenty-seven patients were divided into two groups. The first group of patients were those with functional disturbances of the sympathetic nervous system, characterized by localized hyperhidrosis involving the palms, soles, and axillae, alone or conjointly. This condition is usually symmetrical; the affected parts are cold and clammy to the touch, and the skin is frequently macerated, sodden, and thickened.

REPORT OF CASES

Mrs. E. P., a 40-yr.-old housewife, had complained of hyperhidrosis for 15 yr. This condition was present the year round and was usually associated with anxiety or fatigue. For example, during a 10-min. business conversation on the telephone, perspiration saturated her underclothing, and several large handkerchiefs were needed to hold the receiver. During a card game perspiration from her palms wet the cards, and axillary sweat dripped from her elbows.

Physical examination revealed that the hands were cold, clammy, and wet with perspiration, and the axillary skin was moist and erythematous. X-ray treatments to the axillae were ineffective. During the first week she was treated conservatively, with 25 mg. of banthine® bromide three times daily. Six hours after taking her first dose her hands became warm, but sweat continued to form. During the next three weeks the dosage was gradually increased until perspiration was no longer evident. The axillary dermatitis cleared during the third week, at which time she noted transient dryness of the mouth, which has not recurred. She is now taking one 50-mg. tablet every four hours and has been instructed to take an additional tablet 45 min. before anticipated stress. She has been on this dosage regimen for 10 wk. with no further evidence of hyperhidrosis even under severe strain.

The second, and larger, group of patients were those with several common dermatoses, such as contact dermatitis of the hands, vesicular eruptions of the hands and feet (dyshidrosis), or intertrigo. Varying degrees of excessive sweating accompanied each of these conditions. Patients with an erythematous vesiculopapular contact dermatitis of the hands were chosen because the irritating properties of palmar

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1. Grimson, K. S.; Lyons, C. K.; Watkins, W. T., and Callaway, J. L.: Successful Treatment of Hyperhidrosis with Banthine,® J. A. M. A. **143**:1331 (Aug. 12) 1950.

sweat frequently prolong the period of recovery. Another type of contact dermatitis treated with banthine® bromide was similar to that described by Blaisdell and Schwartz.[2] This is a recurrent vesicular eruption of the hands and fingers characterized by pearly translucent vesicles without erythema, accompanied by excessive sweating, and developed from a "chronic irritation sustained in either industrial or private life." Patients with recurrent, pruritic, deeply situated vesicles of the hands and feet but with no evidence of fungous infection were also given banthine® bromide. These vesicles were typical of dyshidrosis, which is a persistent disease, accompanied by hyperhidrosis, and believed to be a psychosomatic dermatosis.[3] Patients with intertrigo were also selected because friction or external irritants stimulate the regional sweat glands. The increased production of sweat macerates the skin, and an exudative type of dermatitis follows.[4]

M. B., a 44-yr.-old business man, had complained of recurring pruritic vesicles on the palms and fingers of four-to-five years' duration, which were severer in warm weather. Under emotional strain he had noted excessive sweating of the palms, soles, and axillae.

Physical examination revealed deep, symmetrical, vesicular lesions of the palms and fingers with a superimposed erythematous dermatitis. The hands were warm but moist and the axillae wet with perspiration. He was given 25 mg. of banthine® bromide three times daily with little clinical improvement. The dosage was rapidly increased to 50 mg. every four hours. His hands became warm and dry, the vesicular eruption subsided, and the dermatitis of his hands cleared completely four weeks after banthine® therapy was initiated. Previous attacks of the same disorder had persisted for 12 wk. or more despite x-ray therapy and topical applications.

Types of Diseases, Number of Patients, and Clinical Results with Banthine® Bromide

Diseases Treated with Banthine® Bromide	Number of Patients	Clinical Results		
		Marked Improvement	Moderate Improvement	Slight Improvement
Hyperhidrosis	5	5	0	0
Contact dermatitis associated with excessive sweating	10	8	1	1
Vesicular eruptions of the hands and feet (dyshidrosis)	6	4	2	0
Intertrigo	6	3	2	1
Totals	27	20	5	2
Results	..	74%	19%	7%

During the first week patients were given 25 to 50 mg. three times daily. Each week the daily dosage was increased 100 mg. until the desired clinical results were obtained. The maximum daily dose given to two patients was 450 mg.

RESULTS

Observational studies were made on 27 patients for an average of eight weeks, the maximum period of observation being 16 weeks and the minimum period six weeks. In each of the five patients treated for hyperhidrosis there was marked improvement with complete remission of symptoms (Table). Ten patients were

2. Blaisdell, J. H., and Schwartz, J. H.: Recurrent Resistant Vesicular Eruptions of the Hands, Arch. Dermat. & Syph. **51**:365 (June) 1945.

3. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948, p. 401.

4. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948, p. 149.

treated for contact dermatitis associated with excessive sweating. Eight of these patients showed marked improvement with decreased erythema and no further vesicle formation. One patient had moderate improvement and another had only slight improvement. Six patients were treated for vesicular eruptions of the hands and feet (dyshidrosis). Four had marked improvement with dryness of the areas and disappearance of the vesicles, and two patients showed moderate improvement. Of the six patients treated for intertrigo, three had marked improvement with diminished erythema and itching, two had moderate improvement, and one patient had only slight improvement. Seventy-four per cent of all patients showed marked improvement with banthine®-bromide therapy; 19% had moderate improvement; only 7% had slight improvement.

The daily dosage of banthine® varied between 100 mg. and 200 mg. Initial dryness of the mouth was noted by seven patients and transient blurring of vision by three. Temporary urinary retention was noted in one patient.

COMMENT

Excessive sweating in patients with uncomplicated hyperhidrosis can be effectively controlled by banthine® bromide. These clinical findings corroborated those first described by Grimson and his associates. Moreover, the cases of contact dermatitis associated with excessive sweating responded more quickly to the combined use of local applications and banthine® given orally. Although the exact etiologic factors of the various vesicular eruptions of the hands, fingers, and feet are controversial, the authors observed a more rapid involution of the vesicles when banthine® therapy was used.

It is our impression that banthine® is of definite value in the treatment of certain diseases of the sweat glands. The drug is being used in two patients with hydradenitis axillaris suppurativa with promising effectiveness. In two other patients with menopausal symptoms complicated with severe sweating, banthine® has produced marked relief of perspiration which the optimum estrogenic regimen was unable to control. In one patient with nocturnal sweating so severe as to necessitate a change of nightclothes every two hours, banthine® produced an abrupt remission of sweating. These results are sufficiently encouraging to warrant a more comprehensive clinical evaluation.

Certainly banthine® bromide has been shown to be an effective adjunct in the treatment of hyperhidrosis and of several common dermatoses.

SUMMARY

Twenty-seven patients received banthine® bromide (beta-diethylaminoethyl xanthene-9-carboxylate methobromide) for hyperhidrosis, contact dermatitis of the hands associated with excessive sweating, vesicular eruptions of the hands and feet (dyshidrosis), or intertrigo. Seventy-four per cent of the patients had marked improvement, 19% had moderate improvement, and 7% had slight improvement.

915 Nineteenth St., N. W.

IDIOPATHIC HYPERLIPEMIA WITH SECONDARY XANTHOMATOSIS

Report of a Case

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IN A RECENT publication [1] Thannhauser stated, "The clinical syndrome of idiopathic hyperlipemia in adults with secondary eruptive xanthoma, occasionally accompanied by glycosuria, hitherto was not established as a clinical entity but often confused with hyperlipemia in severe untreated diabetes and accordingly classified as 'xanthoma diabeticorum' or 'diabetic hyperlipemia.'"

The term hyperlipemia as used here indicates an opaque, milky blood serum in which the neutral fat content is markedly increased; cholesterol and other lipids are generally elevated to a lesser degree. Hyperlipemia may be idiopathic or associated with, and probably due to, other diseases. In both instances xanthoma may appear or "erupt" when there is a high degree of lipemia and regress when it subsides.

Since the occurrence of xanthoma in idiopathic hyperlipemia is a manifestation of the underlying hyperlipemia, its appearance clinically and histologically is the same as that of xanthoma diabeticorum. The lesions are discrete papules, generally pinhead sized, but may be as large as a pea. They are light yellow and are surrounded by a hyperemic or inflammatory zone. The latter may disappear when the xanthomas have been present for some time, at which point the picture is often difficult to distinguish from xanthoma tuberosum. The fine papules may exhibit a golden top and give the false impression of containing pus or fluid. The eruption tends to develop suddenly and may involve the entire body, but the buttocks and the extensor surfaces of the extremities are the sites of predilection. The blood serum is milky in appearance, owing to a marked increase in neutral fat. Histologically, foam cells are sparsely distributed among bundles of fibrous tissue; Touton giant cells are absent. Sufficient data have not yet been collected to determine the course and prognosis of the disease. Involvement of the coronary arteries has not been reported.

Idiopathic hyperlipemia with secondary xanthoma can be distinguished from xanthoma diabeticorum by the clinical response to a low-fat diet and to insulin treatment. In the former the hyperlipemia is reduced by a diet low in fat and is

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1. Thannhauser, S. J.: Lipidoses: Diseases of the Cellular Lipid Metabolism, ed. 2, New York, Oxford University Press, 1950, p. 214.

not affected by insulin. In xanthoma diabeticorum, however, in which a disturbance of the carbohydrate metabolism exists and severe diabetes is always present, no response is obtained with a low-fat diet, but insulin controls the diabetes and consequently reduces the degree of lipemia to normal.

The inflammatory appearance of the secondary xanthomas, their regression on a low-fat diet, and the markedly elevated neutral-fat level of the blood serum with its resultant milky appearance are the features which differentiate this condition from xanthoma tuberosum.

The case presented in this paper is the first record of this rare condition in dermatologic literature. Fifteen cases have, however, been reported in the medical literature.[2] Of these, nine were in children ranging in age from two to 12 yr. Secondary xanthoma occurred in three of the adults and in four of the children.

REPORT OF A CASE

S. D., a 36-yr.-old white man, first noted the rapid development of yellowish nodular lesions on his trunk and extremities in 1948. A glucose-tolerance test was done at this time and results were normal. Similar lesions continued to appear, and the older ones increased somewhat in size. There were no other symptoms. In June, 1949, when the patient was first seen, there were numerous (20 to 30) pinhead-to-pea-sized, yellowish, nodular lesions distributed over the buttocks, sides of the chest, the thigh, and extensor surfaces of the elbows and knees. They were painless, round, smooth, and attached to the skin but not to the underlying tissue. A xanthomatous nodule was present on the right iris, and there were scattered faint clusters of yellow-orange material on the left iris. There was no evidence of lipemia retinalis, and a complete physical examination revealed no significant abnormalities. Other relevant data included an increase of 15 lb. (6.8 kg.) in weight in the preceding two years. The patient's father died at the age of 65 of a myocardial infarction, and his mother, a diabetic, died at 62 of a second cerebrovascular accident. Four siblings were living and well. Laboratory and other examinations, which were done in order to rule out diabetes, hypothyroidism, primary familial cholesteremia, and xanthoma disseminatum, included lipid studies of the blood serum, a glucose-tolerance test, basal metabolic rate, roentgenograms of the skull, electrocardiogram, and biopsy. The electrocardiogram, results of a glucose-tolerance test, and roentgenograms of the skull were normal. The basal metabolic rate was + 16. Biopsy of a xanthomatous nodule showed groups of bands of light-staining foam cells with relatively small nuclei and abundant cytoplasm in the upper and mid cutis. Touton cells were absent. The blood serum was silky in appearance, and chemical examination by Bloor's test revealed total lipid and total cholesterol values of 2,164 and 974 mg. per 100 cc., respectively. Treatment was entirely dietary in nature; 1,600 calories were allowed daily, and of these only 90 were derived from fat. All lesions began to recede within one month after treatment was begun and disappeared seven months later. After the third month of therapy the serum was clear, and the total cholesterol was 222 mg. per 100 cc. Blood-chemistry studies at this time, performed at the New England

2. Bürger, M., and Grütz, O.: Über hepatosplenomegalie Lipoidose mit xanthomatösen Veränderungen in Haut und Schleimhaut, Arch. f. Dermat. u. Syph. **166**:542, 1932. Opitz, H.: Hochgradige Lipämie unklarer Genese bei einem 12jährigen Knaben, Deutsch. med. Wchnschr. **61**:88 (Jan. 18) 1935. Franklin, S. M.: Splenomegaly with Lipemia, Proc. Roy. Soc. Med. **30**:711, 1937. Bernstein, S. S.; Williams, H. H.; Hummel, F. C.; Shepard, M. L., and Erikson, B. N.: Metabolic Observations on a Child with Essential Hyperlipemia, J. Pediat. **14**:570, 1939. Holt, L. E., Jr.; Aylward, F. X., and Timbres, H. G.: Idiopathic Familial Lipemia, Bull. Johns Hopkins Hosp. **64**:279, 1939. Goodman, M.; Shuman, H., and Goodman, S.: Idiopathic Lipemia with Secondary Xanthomatosis, Hepatosplenomegaly and Lipemia Retinalis, J. Pediat. **16**:596, 1940. Chapman, F. D., and Kinney, T. D.: Hyperlipemia: "Idiopathic Lipemia," Am. J. Dis. Child. **62**:1014 (Nov.) 1941. Koszalka, M. F., and Levin, J. J.: Idiopathic Hyperlipemia, Ann. Int. Med. **33**:473, 1950. Thannhauser.[1]

Medical Center through the courtesy of Dr. S. J. Thannhauser, revealed a clear serum with the following findings: neutral fat 240 mg. per 100 cc., total fatty acids 530 mg. per 100 cc., total phospholipids 239 mg. per 100 cc., total cholesterol 232 mg. per 100 cc., free cholesterol 56 mg. per 100 cc., and cholesterolesters 176 mg. per 100 cc.

Since February, 1950, no fresh lesions have appeared, and the diet has been unaltered since its inception. The weight fell by 20 lb. (9.1 kg.) during the first eight months of treatment.

SUMMARY

A case of idiopathic hyperlipemia in an adult is presented, and the clinical features which make it an entity, as distinguished from xanthoma diabeticorum and xanthoma tuberosum, are discussed.

55 Rugby Rd. (26).

14 E. 16th St. (26).

RESULTS OF TOPICAL APPLICATION OF CORTISONE IN CONGENITAL SYPHILITIC INTERSTITIAL KERATITIS

Preliminary Report of Two Cases

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THE PURPOSE of this preliminary report is to show the effect of topically applied cortisone in two cases of congenital syphilitic interstitial keratitis. Most syphilologists and ophthalmologists agree that the present therapeutic approach to the treatment of this baffling ocular manifestation of congenital syphilis leaves much to be desired. Penicillin has proved its worth in the treatment of congenital syphilis; in the treatment of syphilitic keratitis, however, penicillin, either alone or combined with artificial fever, frequently fails to bring about rapid and certain resolution of the inflammatory process.

The most recent statistics available show that in the continental United States during 1950 there were 13,646 cases of congenital syphilis reported to the Division of Venereal Disease of the United States Public Health Service.[1] Stokes reviewed 164 cases brought to medical attention because of heredosyphilis; of these 52% had or had had interstitial keratitis, 26% had other types of ocular disease, and only 22% had normal eyes.[2] Stokes states, "for the syphilitic child, interstitial keratitis thus becomes one of the most serious and distressing of symptoms."[2] Because of the relative frequency of interstitial keratitis in the congenitally syphilitic child, this condition is a serious problem. One more important but often overlooked factor that may be considered is that a great amount of time is lost from school, which occurred in both the cases we studied.

In view of these facts, we decided to attempt the treatment of congenital syphilitic keratitis by means of the topical application of cortisone. Numerous favorable reports have recently appeared in the literature in which the parenteral use of cortisone and corticotropin (ACTH) has been of value in many hitherto

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From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman), and the Service of Dermatology and Syphilology of Bellevue Hospital (Dr. Frank C. Combes, Chief of Service).

1. Statistics: Venereal Disease Cases and Rates per 100,000 Population, Continental United States Civilians, Fiscal Year 1950, J. Ven. Dis. Inform. **32**:24 (Jan.) 1951.

2. Stokes, J. H.; Beerman, H., and Ingraham, N. R.: Modern Clinical Syphilology, ed. 3, Philadelphia, W. B. Saunders Company, 1944, p. 1114.

recalcitrant eye disorders. Steffensen, Olson, Margulis, Smith, and Whitney [3] reported on the successful treatment of congenital syphilitic interstitial keratitis in one case in which both corticotropin (ACTH) and cortisone were used parenterally, after which cortisone was applied topically. In their summary they stated that it was impossible to evaluate the result because of the two drugs used and the different modes of administration. Geddes and McCall [4] have recently reported on the favorable response of syphilitic keratitis to the parenteral administration of cortisone.

METHOD

One drop of cortisone acetate (ophthalmic suspension), 2.5% strength (25 mg. per cubic centimeter),[5] was dropped into the conjunctival sac of the affected eye every hour during the waking hours (7 a. m. to 9 p. m.). Ophthalmic examination, including slit lamp and measurements of visual acuity, were done on each of these patients previous to starting this therapy and again after the completion of the therapy.

REPORT OF CASES

Case 1.—C. M., a 15-yr.-old Puerto Rican girl, gave a history of photophobia and tearing with gradual loss of vision in her right eye since her return to school in September, 1950. There was no history of previous ocular involvement; nor was there any history of previous treatment of syphilis. She was admitted to Bellevue Hospital on Oct. 2, 1950, at which time her serologic tests showed the following reactions: Wassermann, 4+; Mazzini, 4+; Kahn, 4+ (512 units); VDRL, positive (1:80). The cerebrospinal fluid findings were normal.

At the time of admission, Sept. 2, 1950, the vision in the right eye was limited to perception of hand movements at a distance of 1 ft. (33 cm.). Slit-lamp examination revealed limbal infiltration at 12 o'clock, and superficial as well as deep fascicular vascularization into the stroma. There was also generalized infiltration with localized areas of deep infiltration, mutton fat, keratic precipitates, and thickening of the cornea. There was no inflammatory reaction in the anterior chamber and no iris involvement. The fundus was not seen.

Penicillin therapy was started on Oct. 17; 900,000 units of penicillin procaine were given intramuscularly daily for nine days for a total of 8,100,000 units. On Oct. 26, the ninth day of penicillin therapy, ophthalmologic examination showed no subjective or objective change. No treatment other than 1% solution of atropine, one drop three times a day, was given for 10 days, at the end of which time re-examination of the eye showed no improvement. There was extensive vascularization and infiltration still present. At this time, Oct. 26, 1950, one drop of ophthalmic suspension of cortisone 2.5% was instilled in the eye every hour from 7 a. m. to 9 p. m. In 24 hr. there was subjective improvement with decreased pain and photophobia. On Oct. 29, the fourth day of cortisone therapy, ophthalmologic examination showed the vision in the right eye to be 20/100, vascularization was much decreased, and the infiltration was clearing. There still were large mutton-fat keratic plaques present. The fundus was not seen. Cortisone therapy was continued for a total of 10 days.

Examination of the right eye 10 days after cortisone therapy showed continued improvement. The visual acuity had remained at 20/100 in the right eye; slit lamp revealed that the infiltrates that remained were fewer in number and softer.

Case 2.—E. E., a Negro girl, aged 13, with bilateral involvement of her eyes due to congenital syphilitic interstitial keratitis, was admitted to Bellevue Hospital on Nov. 1, 1950. Her

3. Steffensen, E. H.; Olson, J. A.; Margulis, R. R.; Smith, R. W., and Whitney, E. L.: The Experimental Use of Cortisone in Inflammatory Eye Disease, Am. J. Ophth. **33**:1033-1040 (July) 1950.

4. Geddes, A. K., and McCall, M. F.: Interstitial Keratitis Treated with Cortisone, Canad. M. A. J. **63**:601 (Dec.) 1950.

5. The cortisone acetate (ophthalmic suspension), 2.5% strength (25 mg. per cubic centimeter), was supplied by Merck & Company, Inc., through the courtesy of Dr. Augustus Gibson, Executive Director, Medical Division.

history revealed that in February, 1950, she had experienced pain and discomfort, redness, and excessive lacrimation of both eyes when she went out of doors or looked at a light; after this acute phase, the attack subsided, but she noticed impairment of her vision. In July, 1950, she had a further attack, at which time she sought medical attention and was given biweekly injections of penicillin of undetermined amount for three weeks at another institution. On Aug. 8, 1950, she was admitted to Bellevue Hospital because of her increasing visual impairment and photophobia. At this time she was given 19,000,000 units of penicillin procaine and discharged with moderate improvement, which continued following her penicillin therapy; but vascularization of the cornea failed to halt. She was readmitted to Bellevue Hospital on Nov. 1, 1950, at which time she was able to read, which she was unable to do prior to penicillin therapy. However, both corneas showed opacities and marked vascularization by slit-lamp examination.

Results of routine laboratory investigation were within normal limits. Serologic tests showed the following reactions: Mazzini, 4+; Wassermann, 4+, and Kahn, 4+ (1:128).

On Nov. 8, prior to the administration of topical cortisone, ophthalmic examination showed visual acuity in the right eye 16/70 and in the left eye 16/50. Slit-lamp examination revealed diffuse ground-glass infiltration with mottled densities and numerous blood vessels. The process was more extensive in the right eye than in the left. The iris was normal in the left eye but not well visualized in the right.

On Nov. 15, while still receiving cortisone, the patient was examined in the department of ophthalmology; their finding was definite subjective improvement apparent. Visual acuity test revealed no change in the right eye, but the left eye showed some improvement (right eye 16/70; left eye 16/40). Slit-lamp examination revealed no change in the right eye, but in the left cornea there was definite clearing of the infiltrates. Administration of cortisone ophthalmically was stopped after 10 days of therapy.

On Nov. 29, twenty-one days after the start of therapy, visual-acuity examination revealed moderate bilateral improvement (right eye 16/50; left eye 16/30). Slit-lamp examination revealed that moderate improvement was maintained and that there were fewer infiltrates present.

COMMENT

This preliminary report has demonstrated that cortisone acetate, when used topically, was beneficial in the two cases of congenital syphilitic interstitial keratitis studied. In the opinion of senior syphilologists who had followed these cases, the rapid resolution of the inflammatory process was due to the topically applied cortisone. This observation was further substantiated by the ophthalmologic examinations. The more favorable response obtained in Case 1 might be explained by the fact that the inflammatory process was treated within two months of its onset, whereas in Case 2 nine months had elapsed before cortisone therapy was instituted. In cases of congenital syphilitic interstitial keratitis of long standing, which exhibit thicker keratic plaques and less vascularization of the cornea than the acute phase of this condition, reaction might be more favorable if the technique suggested by Raphael Koff and co-workers were used.[6] This procedure as described is not difficult; it entails the subconjunctival injection of cortisone. At the present time we are in no position to explain the therapeutic action of cortisone when applied topically. The recent literature dealing with the action of cortisone in inflammatory processes of the eye[7] and in diseases of the eye in which hypersensitivity plays a

6. Koff, R.; Rome, S.; Kasper, R.; Commons, R. R.; Button, R., and Starr, P.: Subconjunctival Injection of Cortisone in Iritis, J. A. M. A. **144**:1259-60 (Dec. 9) 1950.

7. Jones, I. S., and Meyer, Karl: Inhibition of Vascularization of the Rabbit Cornea by Local Application of Cortisone, Proc. Soc. Exper. Biol. & Med. **74**:102-104 (May) 1950. Woods, A. C., and Wood, R. M.: The Action of ACTH and Cortisone on Experimental Ocular Inflammation, Bull. Johns Hopkins Hosp. **87**:482-504 (Nov.) 1950.

role [8] suggests several hypotheses on the basis of experimental work done. However, in the two cases described in this report events indicate that the topically applied cortisone exerted its effect at a cellular-tissue level. Cortisone used locally has several advantages over the parenteral or oral administration of the drug: (1) In the small dosages used, the drug is relatively inexpensive, and (2) there were no undesirable systemic or physiologic alterations in the cases studied.

SUMMARY

1. Two patients with congenital syphilitic interstitial keratitis were treated with cortisone applied topically.

2. The results in Case 1 were more striking than in Case 2. The first patient was treated within two months of the onset of ocular symptoms; the second was not treated until some nine months following the first manifestations of disease. This difference in time may explain the difference in the results obtained.

3. Treatment is inexpensive; the patient is ambulatory, and there is little or no danger of physiological alteration.

4. The exact mechanism of action of cortisone when used topically is unknown.

5. Penicillin, with or without artificial fever therapy, remains the method of choice in the treatment of congenital syphilis or of its sequelae. Cortisone used topically or subconjunctivally may well be a useful therapeutic adjuvant in the treatment of congenital syphilitic interstitial keratitis.

999 Fifth Ave. (28).

Drs. Evan W. Thomas and Simeon E. Landy gave advice and assistance in this study.

Dr. Arthur G. Devoe, Professor and Chairman of the Department of Ophthalmology, New York University Post-Graduate Medical School, and members of his staff did the ophthalmological examinations.

8. Harvey, A. M.; Howard, J. E., and Kattus, A. A.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Certain Diseases of the Eye in Which Hypersensitivity Plays a Role, Bull. Johns Hopkins Hosp. **87**:461-481 (Nov.) 1950.

OCCUPATIONAL LEUCODERMA FROM RUBBER DUST AND DEBRIS

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OLIVER, Schwartz, and Warren [1] were the first to report their observation that leucoderma may occur as a result of occupation. In their patients areas of depigmentation developed after contact with rubber containing the antioxidant monobenzyl ether of hydroquinone. Since then, W. D. McNally [2] presented a number of similar cases of depigmentation in Negro workers. Peck and Sobotka [3] discussed in great detail the experimental and physiochemical aspects of this pigmentary disturbance. Spencer [4] later recorded additional cases of leucoderma due to "agarite alba," the trade name of the antioxidant monobenzyl ether of hydroquinone.

Recently we have encountered nine cases of leucoderma in white workers who came in contact with dust and debris containing "agarite alba." These workers are machine operators who sew thin rubber strips onto asbestos pads. In the course of this operation a heavy alkaline oily dust is created, which settles down upon the face, hands, and forearms of the workers and in some of the workers causes areas of depigmentation.

REPORT OF CASES [5]

On Aug. 17, 1950, Mrs. R. S., aged 50, white, who is employed as a machine operator working on asbestos ironing pads, was referred to us for examination.

Her work consisted in sewing rubber strips on asbestos pads. She had been doing similar work with impunity for the last six years, but one year ago she began to work with oiled thread, and the exposed parts of the skin were showered with droplets of oil. About six months later

From the Department of Dermatology, Northwestern University Medical School, Dr. Herbert Rattner, Chairman.

1. Oliver, E. A.; Schwartz, L., and Warren, L. H.: Occupational Leukoderma, J. A. M. A. **113**:927-928 (Sept. 2) 1939. Schwartz, L.; Oliver, E. A., and Warren, H. L.: Occupational Leukoderma, Pub. Health Rep. **55**:1111-1130 (June 31) 1940. Schwartz, L.; Oliver, E. A., and Warren, H. L.: Occupational Leukoderma, Arch. Dermat. & Syph. **42**:993-1014 (Dec.) 1940.

2. McNally, W. D.: Depigmentation of Skin by Rubber Gloves, Indust. Med. **8**:405-410 (Oct.) 1939.

3. Peck, S. M., and Sobotka, H.: Effect of Monobenzyl Hydroquinone on Oxidase Systems in Vivo and in Vitro, J. Invest. Dermat. **4**:325-329 (Aug.) 1941.

4. Spencer, G. A.: Leukoderma Produced by Antioxidants: Report of Cases, Arch. Dermat. & Syph. **58**:215-219 (Aug.) 1948.

5. These cases were presented at the meeting of the Chicago Dermatological Society, Oct. 18, 1950.

the patient noticed areas of depigmentation on the hands, forearms, forehead, neck, and dorsa of the feet. Upon exposure to sunlight the white areas became accentuated because of the darkening of the normal surrounding skin. It was for this bizarre pattern of depigmentation that she sought medical opinion.

The patient was a well-nourished middle-aged white woman who presented depigmented macules of various sizes and shapes on the dorsa of the hands, the forearms, arms, neck, face, and feet. Physical examination and routine laboratory examinations did not reveal any other pathologic findings.

The raw materials with which this patient came in contact during her work were white elastic strips, blue elastic strips, asbestos pads, white oiled thread, blue oiled thread, and machine

Leucoderma from contact with oil droplets containing "agarite alba."

oil. Patch tests were performed with these materials and elicited a positive reaction only to the blue elastic. The dust and debris collected in the plant also produced a positive reaction. This dust consisted of asbestos dust, oil, rubber particles, and thread particles.

Mrs. C. H., a white woman, aged 40, presented a similar but milder picture. Seven other white workers in this same plant had similar complaints.

COMMENT

Since rubber deteriorates rapidly upon exposure to air by combining with oxygen, antioxidants are usually added. "Agarite alba" is the trade name of a popular antioxidant which is apparently a monobenzyl ether of hydroquinone. The anti-

oxidant is dissolved out of the rubber by perspiration and may be absorbed by the skin, and, especially in the presence of an alkaline skin reaction, it is apt to create areas of depigmentation.

CONCLUSIONS

The development of leucoderma in these cases was unusual in that in these nine white women workers leucoderma occurred not from direct handling of rubber but rather from contact with oil droplets containing the antioxidant material. Leucoderma developed in only nine out of 200 workers, all of them white and similarly exposed. Apparently other factors besides mere contact are needed to produce this phenomenon.

1 N. Pulaski Rd.

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EVALUATION OF A NEW DRUG FOR TOPICAL THERAPY OF TINEA CAPITIS

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THE INCREASE in the incidence of tinea capitis of the anthropophilic type, which has often assumed epidemic proportions during the past several years, has clearly demonstrated the need for a simplified form of effective treatment.

Many therapeutic approaches have been abandoned as unsatisfactory, and others have met with varying degrees of success. For example, the use of trichophytin injections produced equivocal results and was discarded.[1] Similarly, the topical administration of hormones proved of only dubious value.[2] The proper application of trimethyl cetyl ammonium pentachlorphenate (T. C. A. P.)[3] required diligent care for several hours daily, and the use of this product was therefore relinquished as impracticable. While fatty-acid compounds have merits in the treatment of mycoses of the glabrous skin, they are ineffectual against tinea capitis. Salicylanilide ointment is attended by better results, but it still leaves much to be desired. Against this background, we welcomed the opportunity to evaluate clinically the dihydrochloride of 2-dimethylamino-6-(beta-diethylaminoethoxy)-benzothiazole,[4] which, according to Grunberg and his associates[5] is distinguished by great anti-

From the Department of Dermatology and Syphilology, Newark Board of Health Clinics.

1. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 2, Chicago, The Year Book Publishers, Inc., 1943.

2. Poth, D. O., and Kaliski, S. R.: Estrogen Therapy of Tinea Capitis: Preliminary Report, Arch. Dermat. & Syph. **45**:121-128 (Jan.) 1942. Lewis, G. M.; Hopper, M. E., and Reiss, F.: Ringworm of Scalp: Clinical Data on Recent Cases; Experiences with Local Endocrine Therapy, J. A. M. A. **132**:62-65 (Sept. 14) 1946.

3. McKee, G. M.; Herrmann, F., and Karp, F. L.: New Treatment for Anthropophilic Tinea Tonsurans (Microsporon Audouini): Preliminary Report, J. Invest. Dermat. **7**:43-52 (Feb.) 1946.

4. The materials used in this study were supplied by Hoffman-LaRoche, Inc., Nutley, N. J., through the cooperation of Dr. Leo A. Pirk. They were furnished first under the code number Ro2-2453 and later under the name of asterol® dihydrochloride. Originally, an ointment and tincture containing 2% of the active agent were employed. As the study progressed this was increased to 5%.

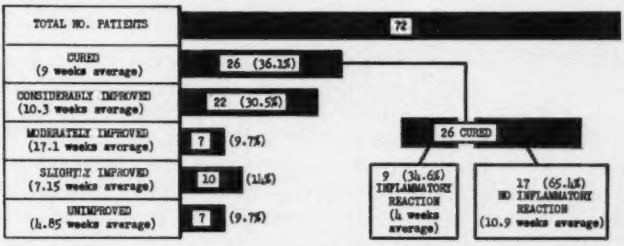
5. Grunberg, E.; Soo-Hoo, G.; Titsworth, E.; Ressetar, D., and Schnitzer, R. J.: Mycological Studies with a New Benzothiazole with Specific Activity Against Dermatophytes, Tr. New York Acad. Sc. **13**:22-27 (Nov.) 1950.

fungal activity in vitro, particularly against dermatophytes of the genera Trichophyton and Microsporum, and which, according to Stritzler and his collaborators,[6] is not a primary irritant and not a potent sensitizer, as gauged by patch tests performed on several hundred patients.

MATERIAL AND METHOD OF TREATMENT

From April 12 to Sept. 30, 1950, a total of 120 patients with tinea capitis applied for treatment at our clinic. For some of them therapy had been instituted elsewhere with other remedies, and their cases were excluded from the series to be presented; several were lost from observation or were transferred to other clinics more conveniently located or to private care, and so only 72 remained whose cases were included in the present study. In the majority of these patients the disease was of considerable duration and severity, with involvement of disseminated patches. There were 59 boys and 13 girls, ranging in age from 1 to 11 yr., with an average age of 7¾ yr. Microsporum audouini was culturally determined as the causative organism in all instances. These children came from the city's most indigent families with a large number of siblings. Home care, if available at all, was likely to be at a minimum.

Our treatment plan may be divided into two equally important phases, one entailing therapeutic and the other prophylactic measures.



Results of asterol® hydrochloride treatment of tinea capitis due to M. audouini. Cured patients had shown no fluorescence on six consecutive examinations under Wood's light. Considerably improved patients had shown no fluorescence on an examination under Wood's light but had not yet had six such examinations.

Therapeutic Regimen.—The hair was clipped as short as possible initially and at weekly intervals. Manual epilation was employed only in very severe cases. Asterol® dihydrochloride was administered three times daily. The tincture was sprayed over the entire scalp to "thorough wetness" in the morning and again during the afternoon. A heavy towel was wrapped tightly around the head to prevent the alcoholic liquid from running into the eyes. At bedtime, after the scalp had been thoroughly washed with ordinary soap or shampoo, asterol® dihydrochloride ointment was applied plentifully and massaged into the scalp, preferably with a soft toothbrush.

Patients were instructed to discontinue medication temporarily when a reaction appeared and to report promptly to the clinic. Inflammatory reactions were treated with wet, warm boric-acid dressings, which were applied three times daily for 20 min.

Prophylactic Regimen.—The children were requested to wear constantly white cloth or stockinet caps, which were to be sterilized after each period of use. In addition, each patient was to carry a boiled cap in his pocket to replace the cap on the head if it were removed.

Parents were instructed to dispose of their children's fuzzy toys, to which infected hairs might easily adhere and thus increase the danger of reinfection. Parents were also told that frequent thorough housecleaning was desirable, particularly in the rooms in which the infected children spent most of their time. Wherever possible, this was to include the use of a vacuum cleaner on the furniture.

6. Stritzler, C.; Fishman, I. M., and Laurens, S.: Treatment of Superficial Fungus Infections with a New Antifungal Agent, Tr. New York Acad. Sc. **13**:31-37 (Nov.) 1950.

Patients were not to attend barber shops, not to share beds, clothing, or combs with siblings or playmates, and not to engage in games, such as wrestling, which would bring them into close contact with other children. However, the patients were permitted to attend school provided they wore skull caps.

Finally, parents were requested to bring presumably noninfected siblings to the clinic at frequent intervals for examination under Wood's light. Even if the result of this examination was negative, asterol® dihydrochloride tincture and ointment was to be applied semiweekly with the objective of thus preventing an infection.

All patients were to report once a week to the clinic, where they were examined regularly under Wood's light. A patient was pronounced cured after six consecutive weekly examinations showed complete absence of fluorescence.

RESULTS

Our results are presented graphically on the accompanying chart. As is seen, 26 patients, or 36.1%, were cured. This includes patients who on six consecutive weekly Wood's-light examinations have shown no fluorescence. Twenty-two patients, or 30.5%, were considerably improved. This category comprises patients who had shown no infected hairs on a Wood's-light examination but had not yet had six consecutive examinations with negative results. Seventeen patients, or 23.7%, were moderately or slightly improved, and seven, or 9.7%, remained unimproved.

The time of treatment required for first Wood's-light examination to reveal no fluorescence in the group of cured patients ranged from two to 17 weeks with an average of 9 weeks, the majority of patients requiring six to 10 weeks of therapy. In general, recovery was rapider in those instances in which there was good cooperation. In case of a relapse before the end of the follow-up period, the time was computed from institution of therapy throughout the period of observation to the second Wood's-light examination showing no fluorescence, which was then followed by five examinations with negative results.

The time of treatment of the unimproved children ranged from three to 8 weeks, with an average of 4.85 weeks. Among these seven children who derived no benefit there was only one who cooperated well.

In 12 children, or 16.7%, folliculitis or a kerion-like reaction developed. Nine of these were cured, and three were considerably improved. Thus, of the 26 children who were cured, nine, or 34.6%, went through an inflammatory phase before they progressed to cure. In these the average period of treatment to attain Wood's-light examination showing no infected hairs was four weeks, as contrasted with almost 11 weeks for those patients who were cured but in whom an inflammatory reaction did not develop.

In two children, or 2.8%, a dermatitis venenata developed. In one case a mild dermatitis, appearing after six weeks of therapy, cleared with discontinuance of treatment, and reappeared with reinstitution of therapy. The reaction subsided again shortly after withdrawal of the medication. Subsequently this patient, who had been considerably improved, was lost from observation. In the other case, a moderately severe dermatitis, appearing after three weeks of therapy, abated with cessation of use of the drug, and returned with resumption of treatment. Application of asterol® dihydrochloride, therefore, was discontinued. Again the dermatitis venenata subsided, and the scalp showed no infected hairs under Wood's light with the clearing of the reaction. A total of six weeks was required before examination under Wood's light revealed no fluorescence. After disappearance of the dermatitis, a patch-test reaction was positive (2+ after 48 hr.).

COMMENT

Ringworm of the scalp is a problem in big cities, with their accumulation of underprivileged people. The anthropophilic type of the disease is notoriously refractory to topical treatment, particularly if there is poor parent cooperation characteristic of destitute families with many children. Because of the impracticability of x-ray treatment if large numbers of children are afflicted, and also because of its inherent hazards, public health agencies and dermatologists have continued their search for a topical remedy which would be effective in a high percentage of cases, which would be easily applicable, and which would be safe in that it would elicit a minimum of untoward reactions. Our study has shown that asterol® dihydrochloride fulfils these requirements.

An incidence of success of 66.6%, including all patients who showed no infected hairs under Wood's light, reflects greater effectiveness than do the results obtained previously with other topical agents in similar groups of children in our clinic. Even if one or another patient in the "considerably improved" group should again show fluorescence under Wood's light in the course of the scheduled re-examinations, the therapeutic efficacy of asterol® dihydrochloride would still far surpass that of the undecylenic-acid-type preparations or of salicylanilide.

Our rate of success approximates and substantiates the results reported by Stritzler and his associates,[6] who, in a series of 61 patients with tinea capitis of the M. audouini type, attained Wood's-light examinations revealing no fluorescence in 43, or 70.4%. However, the incidence of inflammatory reactions, which was 16.7% in our group, was almost twice as high (32.8%) in the series reported by Stritzler and his collaborators. This difference may be due, at least in part, to the fact that our children used a toothbrush for applying medication only once a day, whereas Stritzler's patients were exposed twice daily to such mechanical irritation. Similarly, manual epilation, which was performed daily for all his patients, played a minor part in our regimen. This was predicated on the fear that a procedure as annoying as the extraction of hairs would result in the truancy of many of our children.

Since parents or guardians often did not accompany the patients on their visits to the clinic, an attempt was made to impress upon the older children, both at the clinic and in the schools, the necessity for abiding by certain hygienic measures and for regular application of medication. This, of course, was only partially successful, and the help of school nurses and of orderlies at the clinic was enlisted to apply therapy and to educate parents, some of whom had to be visited at home.

This unrelenting effort of the staff was countered by the lack of insight on the part of many of the parents. Cooperation was so pitifully lacking that, for instance, skull caps which were provided were often either not worn or worn only on the occasion of the child's visit to the clinic. Patients who did wear the caps frequently used them for several days without boiling, removing and replacing them many times in the course of a day.

Against the background of such an unfavorable setting, patients with ringworm of the scalp can be managed as successfully as those in the group presented only by means of an effective medication which is distinguished by great ease of application.

As for the safety of asterol® dihydrochloride, we did not encounter any primary irritation. Contact-type dermatitis was exhibited by two of our patients. In both, the inflammation subsided upon cessation of therapy and appeared again on re-exposure to the drug. A patch test performed on one of these children proved the presence of sensitization to asterol® dihydrochloride.

SUMMARY AND CONCLUSIONS

Seventy-two patients, 59 boys and 13 girls, ranging in age from 1 to 11 yr., with tinea capitis of the anthropophilic type, were treated with asterol® dihydrochloride, a new antifungal compound. Forty-eight children, or 66.6%, showed no infected hairs under Wood's light after therapy. Of these, 26, or 36.1%, had shown no fluorescence on six consecutive Wood's-light examinations, our arbitrarily chosen criterion for cure, and 22, or 30.5%, had shown no infected hairs under Wood's light but have had fewer than six weekly Wood's-light examinations with negative results. Seventeen children, or 23.7%, showed varying degrees of improvement, and seven patients, or 9.7%, showed no improvement. In contrast to much inferior results obtained previously with other antifungal preparations in comparable groups of patients, asterol® dihydrochloride was found effective in a high percentage of cases with tinea capitis due to M. audouini. The drug proved reassuringly safe in that it elicited a minimum of untoward reactions. Since asterol® dihydrochloride is distinguished by ease of application, its use is attended by very gratifying results, also, in the treatment of patients whose parents contribute little cooperation.

190 Clinton Ave. (5).

92 William St. (2).

22 Goldsmith Ave. (8).

CAPILLARY RESISTANCE TESTS

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FOR ALMOST a century medical observers have described the hemorrhagic response to pinching, bruising, and needling the skin. These crude tests were the predecessors of the pressure capillary resistance tests, which have been the subject of considerable investigation in the past half-century, with results that have been diverse and often contradictory. The purpose of this review is to collect and evaluate the literature concerning such tests and to discuss the anatomic, physiologic, and environmental factors which influence capillary resistance. The effects of disease are outside the scope of this study.

The term "capillary resistance" is not as accurate as "cutaneous vascular resistance," but it has the sanction of usage and will be used here. The term "capillary permeability" should be reserved for reference to the passage through the vessel walls of plasma and solutes, not blood cells.

The pressure tests were initiated by Hecht's description of his negative-pressure ("suction") method in 1907.[1] Rumpel and Leede devised their positive-pressure ("stasis" or "tourniquet") method in 1909.[2] The pressure tests act by engorging the small vessels until the blood escapes and forms petechiae. This engorgement is accomplished by raising the intravascular pressure in the stasis test and by lowering the extravascular pressure in the suction tests. Examination of the skin following the test may reveal petechiae visible with the unaided eye, and many minute hemorrhages usually can be seen with the use of a lens, the number seen depending on the strength of the lens used.[3] Most investigators have insisted that the experimentally produced petechiae be large enough to be seen with the naked eye, and some have insisted that they be as large as those appearing spontaneously in purpuric states.[4]

From the Edwin Shaw Sanatorium (Dr. Hare) and the Department of Pathology, University of Louisville School of Medicine (Dr. Miller).

1. Hecht, A. F.: Experimentell-klinische Untersuchungen über Hautblutungen im Kindesalter, Jahrb. Kinderh. **65**:113-131, 1907.

2. Rumpel, T.: Hautblutungen im Scharlach, München. med. Wchnschr. **56**:1404, 1909. Leede, C.: Hautblutungen durch Stauung hervorgerufen als diagnostisches Hilfsmittel beim Scharlach, ibid. **58**:293-295, 1911; Zur Beurteilung des Rumpel-Leedeschen Scharlach-Phänomens, ibid. **58**:1673, 1911.

3. Billing, L.: Über den Einfluss der vergrössernden Hilfsmittel auf die Resultate bei Prüfung der Festigkeit der Hautkapillaren, Upsala lakäref. förh. **40**:389-392, 1935.

4. Copley, A. L.: The Ecchymotic Test for Capillary Hemorrhagic Diathesis, Science **107**:201-202, 1948.

As the limitations of space require the condensation and generalization of detailed information, much of the data presented here are approximations derived by us from the original sources.

TECHNIC

Certain conditions must be observed. The subject should be resting warmly and comfortably. He may be sitting or lying, perhaps preferably the latter. The skin area chosen for the test should be free of local disease or deformity, excessive hair, and edema. It should not be subjected to scrubbing or vigorous washing, to the action of alcohol or ether, or to heating or chilling. Unfortunately, the standard test areas are often damaged by venipunctures and repeated blood-pressure determinations. The interpretation of the results depends heavily on the judgment of the observer. There is a tendency to exaggerate the importance of a mild hemorrhagic response. The snake venom capillary resistance tests [5] will not be discussed, since they are rarely used today.

Positive-Pressure Methods.—The apparatus consists of a sphygmomanometer and a good light. Green light demonstrates the petechiae most clearly. The qualitative methods of Rumpel and Leede and many others have been replaced by the quantitative methods introduced by Göthlin [6] in 1931. These quantitative methods are of two general types:

Type I: Those procedures in which a constant positive pressure is applied by the cuff on the arm for a given time, at the end of which the petechiae found in a measured area on the forearm are counted. The essential details of these are presented in Table 1.

Type II: Those procedures in which is noted the time of the appearance of the petechiae on the forearm while the cuff is inflated at a constant pressure. Information on these tests is presented in Table 2.

Since the two arms may vary in their response, it is probably wise to apply the test to both arms and average the results.[7]

The methods, such as Göthlin's, which employ low pressures are considered too insensitive by most workers. Bexelius, however, doubted the value of using stasis pressures over 70 mm. of mercury since he found that above this pressure arterial flow is impeded and venous pressure does not continue to rise.[8] Barnes [9] warned

5. Peck, S. M.; Rosenthal, N., and Erf, L. A.: Intradermal Venom Reaction: A New Method of Determining Capillary Fragility, Proc. Soc. Exper. Biol. & Med. **35**:614-616, 1937.

6. Göthlin, G. F.: (*a*) A Method of Establishing the Vitamin C Standard and Requirements of Physically Healthy Individuals by Testing the Strength of Their Cutaneous Capillaries, Skandinav. Arch. Physiol. **61**:225-270, 1931; (*b*) Outline of a Method for the Determination of the Strength of the Skin Capillaries and the Indirect Estimation of the Individual Vitamin C Standard, J. Lab. & Clin. Med. **18**:484-490, 1933; (*c*) When is Capillary Fragility a Sign of Vitamin C Subnutrition in Man? Lancet **2**:703-705, 1937.

7. (*a*) Munro, H. N.; Lazarus, S., and Bell, G. H.: The Value of Capillary Strength Tests in the Diagnosis of Vitamin C and Vitamin P Deficiency in Man, Nutrition Abst. & Rev. **17**:291-309, 1947. (*b*) Geschwind, H., and Rundquist, N.: Tests Carried Out on 200 Persons with Göthlin's Method for Determining the Strength of the Skin Capillaries and Statistical Treatment of the Results, Upsala lakäref. förh. **40**:403-420, 1935.

8. Bexelius, G.: Studien über die Blutungstendenz der Hautkapillaren bei künstlicher venöser Stauung, Acta med. scandinav. **80**:281-309, 1933.

9. Barnes, R. H.: Capillary Fragility Studies in Diabetes Mellitus and the Use of Rutin in Diabetic Retinitis, Am. J. M. Sc. **219**:368-375, 1950.

against the use of high positive pressures because of the danger of producing thrombosis, but no instance of this possible complication is known to us. The pressure in the tourniquet must not be allowed to exceed or to approach the systolic blood pressure too closely.

TABLE 1.—*Representative Positive-Pressure Methods—Type I: Constant Pressure, Constant Time*

Author and Year of Publication	Pressure, Mm. Hg	Duration, Min.	Diameter Test Area, Cm.	Location of Test Area (All on Anterior Aspect of Forearm)	Normal Limit of Petechiae in Test Area
Göthlin, 1931, et seq.[6]	35	15	6	Antecubital space	2 *
	50	15	6	Same	6 *
Bexelius, 1933 [8]	80	3	4	Most representative area of petechiae present	5 *
Wright and Lilienfeld, 1936 [10b]	S/D †	15	2.5	Below antecubital space	10
Reid, J.: Glasgow M. J. **136:** 49-50, 1941	80	5	2.5	Antecubital space	14 *
Lewis, L. A.; Schneider, R. W., and McCullagh, E. P.: J. Clin. Endocrinol. **4:** 535-539, 1944	Diastolic blood pressure	3	2.5	Below antecubital space	20
Mallery, O. T., Jr.: Proc. Am. Federation Clin. Res. **2:** 34-35, 1945	80	4	2.5	Below antecubital space	10
Donegan, J. M., and Thomas, W. A.: Am. J. Ophth. **31:** 671-678, 1948	S/D †	5	2.5	Below antecubital space	10
Whitesell, F. B., and Snell, A. M.: J. A. M. A. **140:** 1071-1076 (July 30) 1949	100	5	2.5	Below sphygmomanometer cuff	23
Frommeyer, W. B., and Epstein, R. D.: New England J. Med. **241:** 700-712; 743-751, 1949	S/D †	10	5	Below antecubital space	15
Barnes, 1950 [9]	80	4	6	Area where petechiae most numerous	20 *

* Use of lens indicated (5 to 10 diopters).
† Midway between systolic and diastolic blood pressures.

References to other methods of this type: Difs, H.: Acta med. scandinav., Supp. 110, p. 1, 1940; cited by Munro and others.[7a] Soloff, L. A., and Bello, C. T.: Am. J. M Sc. **215:** 655-659, 1948. Loughlin, W. C.: New York J. Med. **49:** 1823-1824, 1949. Lagergren.[8a] Braestrup.[8c] Madison, F. W., and Squier, T. L.: Wisconsin M. J. **37:** 636-640, 1938. Davis, E.: Lancet **2:** 312, 1940. Levrat, M.: Presse méd. **50:** 353, 1942. Walters, J. D.: Ohio M. J. **41:** 632-633, 1945.

TABLE 2.—*Positive-Pressure Tests—Type II: Constant Pressure, Variable Time*

Author and Year of Publication	Pressure, Mm. Hg	Least Time Considered Normal for Appearance of Petechiae, Min.
Walterhöfer, 1925 [6a,c]	50	5
Wagener, H. P.: Proc. Am. Diabetes A. **5:** 203-216, 1945; Foxworthy, L. R.: Personal communication to authors, 1950	90	4.9 *
Montgomery, H.: U. S. Nav. M. Bull. **46:** 1708-1710, 1946	100	8

* Denotes use of lens while observing the skin.
Reference to another method of this type: Müller, H.: Deutsche med. Wchnschr. **45:** 1275, 1919.

These tests are simple to perform, and the equipment is readily available. The pressure may be uncomfortable. A serious objection to these positive-pressure methods is that they cannot be repeated until the arms have had a rest of one to two weeks.[10] The possible effect on the capillary resistance of hypoxia during the stasis

10. (*a*) Göthlin.[6b] (*b*) Wright, I. S., and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), Arch. Int. Med. **57:** 241-274 (Feb.) 1936.

is probably negligible, although complete anoxia in an extremity for five minutes produces a marked fragility.[11]

Negative-Pressure Methods.—The apparatus consists of a vacuum pump, a manometer, and a suction cup which is applied to the skin and sealed, if necessary, with water or grease. A cup with a diameter of 2 cm. gives a lower capillary resistance value than a 1-cm. cup, but the difference is small.[12] A large cup was used by Tey to provide a sampling of a large surface at once.[13] The test area must be kept constant and described with accuracy. The application of suction must be timed accurately, since a variation of a few seconds will influence the result.[14] Suction prolonged more than two minutes may cause the petechiae to be obscured by edema.[15] Only those petechiae which develop in the center of the area covered by the suction cup are counted. The technics for the performance of the various suction tests fall into three general types:

Type I: Those procedures which seek to find the least amount of negative pressure (sometimes called the "critical resistance") that will produce the required number of petechiae in the stated time. The essential details of these methods are presented in Table 3.

Type II: Those procedures in which is counted the number of petechiae appearing in the center of the suction area after the application of a constant negative pressure for a given time. The size of this central area should be stated but has been generally overlooked. These methods are presented in Table 4.

Type III: Those procedures, after the method of Sack, in which suction is applied at various negative pressures from 10 to 70 cm. of mercury, and the appearance time for the petechiae is noted. A pressure of —10 cm. requires over five minutes to produce petechiae, while a pressure of —70 cm. requires but a few seconds. A curve may be constructed from the results. It is rather difficult to see any theoretical or practical value of this time-consuming procedure, and as a consequence the data from these studies have not been tabulated.[16]

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11. (*a*) Bell, G. H.; Lazarus, S.; Munro, H. N., and Scarborough, H.: Capillary Fragility (Resistance): Negative and Positive Pressure Tests Compared, Lancet **2**:536-538, 1942. (*b*) Lewis, T.: Vascular Reactions of the Skin to Injury, Heart **11**:119-139, 1924. (*c*) Crawford, J. H.: The Influence of the Sympathetic Nervous System on the Capillaries During Passive Congestion, J. Clin. Invest. **7**:527-535, 1929. (*d*) Wiemer, P.: Das Endothelsymptom, Ztschr. ges. exper. Med. **78**:229-245, 1931. (*e*) Bayer, W.: Das Endothelsymptom und seine Beeinflussbarkeit: Die "Endothel-Asthenie," Jahrb. Kinderh. **128**:311-322, 1930.

12. (*a*) Wiemer.[11d] (*b*) Lindquist, N.: Studien über die cutane Capillarresistenz im Kindesalter, Acta pædiat. **20**(Supp. 2):1-167, 1937. (*c*) Frischknecht, W.: Über die Prüfung der Capillarresistenz beim Menschen, Cardiologia **9**:76-105, 1945.

13. Tey, A.: Fragilidad capilar normal humana, Barcelona, Salvat Editores, 1940.

14. Sack, G.: Ein neues Verfahren zur Prüfung der Zerreisslichkeit der kleinen Hautgefässe, Klin. Wchnschr. **17**:1539-1542, 1938.

15. (*a*) Ylppö, A.: Zum Entstehungsmechanismus der Blutungen bei Frühgeburten und Neugeborenen, Ztschr. Kinderh. **38**:32-45, 1924. (*b*) Zahorski, W.: Valeur clinique des recherches sur la résistance et al perméabilité des capillaires sanguins cutanés à l'aide de l'appareil de Gorecki-Zahorski, Sang **14**:442-452, 1940.

16. (*a*) Sack.[14] (*b*) Sack, G.: Über die normale Zerreisslichkeit der kleinen Hautgefässe, Klin. Wchnschr. **18**:1341-1343, 1939. (*c*) Schaefer, W.: Untersuchungen über die Gefässzerreisslichkeit bei internen Erkrankungen, Ztschr. ges. exper. Med. **108**:725, 1941. (*d*) Abel, G.: Über Unterschiede der Capillarresistenz und der Körperoberfläche, Deutsche Arch. klin. Med. **191**:60-69, 1943. (*e*) Monod, R., and Cara, M.: Une methode d'investigation de l'état des capillaires: l'effect vantouse, Compt. rend. Soc. biol. **139**:133-136, 1945. (*f*) Goupil, A.: Contribution à l'étude de la résistance capillaire chez les tuberculeux pulmonaires, Paris méd. **37**:407-408, 1947.

Methods for the study of suction effects by skin microscopy have been presented by Bergara and Bergara [17] and Cutter and Marquardt.[18]

TABLE 3.—*Representative Negative-Pressure Methods—Type I: Constant Time, Variable Pressure*

Author and Year of Publication	Diameter of Cup, Cm.	Suction Time, Min.	Number of Petechiae Permitted	Skin Area Tested	Lowest Normal CR, Cm. Hg
Mengler, 1930 [48f]	3.5	1	1	Forearm: anterior surface	20
				Infraclavicular space	10
von Borbely, 1930 [87b]	2	1	2	Forearm: anterior surface	18
				Infraclavicular space	14
Dalldorf, 1933 [86b]	1	1	1	Arm: outer surface	20
Anderson and others, 1936 [86c]	1	1	1	Arm: upper, outer surface	14
				Arm: upper, inner surface	10
Armentano, L.: Ztschr. ges. exper. Med. 97: 630-639, 1936	2	1	2	Infraclavicular space	18
Jersild, T.: Lancet 1: 1445-1447, 1938	2.5	1	2	Supraclavicular space	15 *
Franke, 1940 [88]	2	1	2	Arm: upper, outer surface	18
				Supraclavicular space	12
Brown, 1940 [85c]	1	1	1	Below antecubital space	15
Rudel, 1941 [87c]	2	1	2	Arm: middle, outer surface	20
Diem, 1946 [83a]	2	1	2	Infraclavicular space	12
Regli and Stamphli, 1947 [80b]	2	1	4	Supraclavicular space	6

* Use of lens indicated.

References to other methods of this type: Hecht.[1] Göthlin.[6a] Wiemer.[114] Tey.[12] Liebmann and others.[19] Bayer.[82a] Elliott and Whipple.[82b] Holland.[27] Bayer.[82b] Maloney.[82] Brock and Malcus.[84] Rossman.[44b] da Silva-Mello.[83b] Scarborough.[60b] Frericks and others.[85d] Lewis and Harmer.[65] Brewer.[87b] Galmiche.[67c] Weld.[78] Abt and others.[82d] Cutter, I. S., and Johnson, C. A.: J. A. M. A. 105: 506-506 (Aug. 17) 1935. Adant, M.: Compt. rend. Soc. biol. 123: 130, 1936. O'Hara, P., and Hauck, H.: J. Nutrition 12: 413-427, 1936. Schultz, M. P.: J. Clin. Invest. 15: 385-391, 1936. Sloan, R. A.: J. Lab. & Clin. Med. 23: 1015-1026, 1938. Ralli, E. P., and Friedman, G. J.: Ann. Int. Med. 11: 1996-2006, 1937. Levcowich, T., and Bacheider, E. L.: J. Nutrition 23: 397-408, 1942. Dieckmann, W. J.; Akbasli, Z., and Aragon, G. T.: Am. J. Obst. & Gynec. 57: 711-716, 1949.

TABLE 4.—*Representative Negative-Pressure Methods—Type II: Constant Pressure, Variable Petechial Counts*

Author and Year of Publication	Diameter of Cup, Cm.	Suction Time, Min.	Negative Pressure, Cm. Hg	Skin Area Tested	Normal Limit of Petechiae
Falconer, E. H.; Epstein, N. N., and Wever, G. K.: Arch. Int. Med. 58: 496-511 (Sept.) 1936	1	1	20	Arm: outer surface above elbow	6
Lassner, 1940 [80c]	2	1	60	Forearm: anterior surface	16
Mallery, O. T., Jr.: Proc. Am. Federation Clin. Res. 2: 34-35, 1945	1.5	1	15	Arm: upper, inner surface	2
Aggeler and others, 1946 [82c]	1	1	20	Arm: upper, outer surface	10
McManus, J. F., and Landrigan, F. L.: Proc. Am. Federation Clin. Res. 3: 51-52, 1947; McManus, J. F.: Personal communication to authors, 1949	1	1	20	Antecubital space	8
Hein, 1948 [40f]	2	2	18	Supraclavicular space	6
Schweppe and others, 1949 [85b]	1	0.5	Trials at 10, 20, 30, 40, and 50	Forearm: anterior surface	Total of 30 in all 5 trials

References to other methods of this type: Tey.[12] Zahorski.[16b] Bergara and Bergara.[17] Dalla Torre and Dusso.[47c] Bartelheimer and Baehrecke.[85b] Beaser and others.[82d] Gunter, M.: Lancet 2: 590-593, 1945. Rinehart, J. F., and Greenberg, L. D.: Ann. Int. Med. 17: 672-680, 1942. McNee, G. Z. L., and Reid, J.: Lancet 2: 538-540, 1942.

The advantages of these tests are that they may be performed quickly, repeated frequently, and applied to most of the skin and mucous membranes. They seem to

17. Bergara, C., and Bergara, R.: Nuevo método para medir la fragilidad do los capilares y su aplicación en la cirugia, Semana méd. **2**:1358-1367, 1939.

18. Cutter, I. S., and Marquardt, G. H.: Studies in Capillary Fragility, Proc. Soc. Exper. Biol. & Med. **28**:113-115, 1931.

have been more satisfactory in pediatric practice. The requirement of special equipment is a disadvantage, and there are objections to the principles of these tests. In "critical-resistance" methods (Type I, negative-pressure tests) only the weakest capillary in the test area is measured, an important criticism not applicable to the methods which obtain multiple petechiae (Type II). Many authors have noted inconsistent results in adjacent areas in some body regions. Several have found that petechiae could be produced by weak suction, while at the same time stronger suction produced none. This phenomenon was attributed to the stoppage of the inflow of blood into the tissue that is compressed into the cup by the stronger vacuum.[19] A correlation of the number of petechiae produced and the amount of vacuum used could not be made by one group of investigators, but this has not been the experience of most workers. It will be shown later how the results are affected by the structure of the skin and the region of the body tested.

A light, accurate, and inexpensive instrument for suction tests has been sorely needed. A currently advertised instrument provides no direct measurement of the suction created, but it is said to be accurate enough for clinical work.[20] Further anatomic exploration is needed to find uniform and protected areas for testing (the axilla has been suggested as an area likely to fulfil these requirements). The Type II negative-pressure tests are the easiest to perform and probably the most useful clinically.

Comparison of the Pressure Tests.—The only successful mathematical correlation made between the results of positive- and negative-pressure tests is that of Jersild and Embly.[21] As a rule, the results are comparable only in a general way. Severe fragility found by the one test is usually confirmed by the other. The mass of conflicting claims and confusing data prevents a definite conclusion concerning the superiority of either. Proponents of the more nearly standardized positive-pressure tests state that these tests are more reliable, but examination of their studies suggests that this assumption is not justified.

In some studies the capillary resistance test has been compared with other tests of the hemostatic mechanisms. The investigators found that only occasionally could they correlate capillary resistance with bleeding times,[22] coagulation times,[22a,c] and

19. Liebmann, J.; Wortis, H., and Wortis, E.: Note on the Lack of Correlation of Capillary Fragility with Vitamin C Content of Blood, Spinal Fluid, and Urine, Am. J. M. Sc. **196**:388-392, 1936.

20. Brown, E. E.: Evaluation of a New Capillary Resistometer: The Petechiometer, J. Lab. & Clin. Med. **34**:1714-1717, 1949.

21. Jersild, T., and Embly, A.: Vergleichende Untersuchungen über Methoden zur Bestimmung der Capillarresistenz, Klin. Wchnschr. **17**:1359-1360, 1938.

22. (*a*) Bayer, W.: Die Endothelasthenie im Neugeborenenalter, Jahrb. Kinderh. **129**:55-62, 1930. (*b*) Bruhl, H.: Beiträge zum Krankheitsbild und zur Behandlung des Morbus maculosus Werlhofii, Ztschr. Kinderh. **54**:158-195, 1932. (*c*) Brown, E. E., and Wasson, V. P.: Capillary Resistance in Rheumatic Children, J. Pediat. **18**:328-336, 1941. (*d*) Scarborough, H.: The Vitamins in Relation to Hemorrhage, Edinburgh M. J. **50**:85-119, 1943. (*e*) Tidy, H. L.: Symptoms and Pathogenesis of the Hemorrhagic Diathesis, Brit. M. J. **2**:1073-1079, 1930. (*f*) Allen, J. G.; Bogardus, G.; Jacobson, L. O., and Spurr, C. L.: Some Observations on Bleeding Tendency in Thrombocytopenic Purpura, Ann. Int. Med. **27**:382-395, 1947.

thrombocyte (platelet) counts.[23] This is to be expected, since the phenomena which these several tests attempt to measure are dependent on one another only in specific instances. Landis [24] and Zahorski [15b] have stated that capillary resistance and capillary permeability are unrelated phenomena and rarely become abnormal together. On the other hand, abnormalities of the two conditions have been found to coexist clinically,[25] and the experiments of Armentano [26] and Holland [27] suggest a close association.

FACTORS WHICH AFFECT THE CAPILLARY RESISTANCE IN THE NORMAL SUBJECT

Vascular resistance depends on the structure and the tone of the small blood vessels, their distribution in the dermis, the strength of the surrounding and supporting tissues, and the thickness and stiffness of the epidermis. The result of the test is the sum of these inseparable factors, all of which must be considered in the evaluation of the capillary resistance.

Constitutional Factors.—It has been postulated that certain persons have hereditary vascular inferiority giving rise to fragility.[28] Body type has been thought to have little influence on capillary resistance.[29]

Age and Sex.—The capillary resistance of the premature but otherwise normal infant is found by suction methods to be low, proportionate to its prematurity and weight.[30] This low capillary resistance is believed due to the underdevelopment of the connective tissues about the cutaneous blood vessels. As the premature infant gains weight and strength the capillary resistance rises correspondingly until it eventually reaches the level of the full-term infant, after which it follows the normal

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23. (*a*) Diem, E.: Über die klinische Bedeutung der Kapillar-Resistenz, Cardiologia **10**:25-56, 1946. (*b*) Elliott, R. H. E., and Whipple, M. E.: Observations on the Interrelationship of Capillary, Platelet, and Splenic Factors in Thrombocytopenic Purpura, J. Lab. & Clin. Med. **26**:489-498, 1940. (*c*) Aggeler, P. M.; Howard, J., and Lucia, S. P.: Platelet Counts and Platelet Function, Blood **1**:472-496, 1946. (*d*) Footnote 22 *a*, *b*, and *f*. (*e*) Franke, H.: Die Capillardichte bei hepato-lienalen Erkrankungen und der Einfluss der Splenektomie, Ztschr. klin. Med. **137**:86-98, 1940. (*f*) Elliott, R. H. E.: The Suction Test for Capillary Resistance in Thrombocytopenic Purpura, J. A. M. A. **110**:1177-1179 (April 9) 1938.

24. Landis, E. M.: Capillary Permeability and the Factors Affecting the Composition of the Capillary Filtrate, Ann. New York Acad. Sc. **46**:713-731, 1946.

25. (*a*) Wiemer.[11d] (*b*) Ylppö.[15a] (*c*) Tidy.[22e] (*d*) Frericks, C. T.; Tillotson, I. G. and Hayman, J. M., Jr.: The Effect of Rutin on Capillary Fragility and Permeability, J. Lab. & Clin. Med. **35**:933-940, 1950.

26. Armentano, L.: Ein neuer Beitrag zur Behandlung der hämorrhagischen Diathesen: Die clinische Bedeutung des Landis-Verfahrens, Ztschr. exper. Med. **107**:9-25, 1939.

27. Holland, G.: Capillardichte und Insulin, Ztschr. ges. exper. Med. **108**:178-185, 1940.

28. (*a*) Bayer.[22a] (*b*) Bayer, W.: Beitrag zu den hämorrhagischen Erkrankungen des Neugeborenen: Die Rolle der Endothelasthenie, Jahrb. Kinderh. **133**:222-238, 1931. (*c*) Sack, G.: Status dysvascularis: Ein Fall von besonderer Zerreisslichkeit der Blutgefässe, Deutsches Arch. klin. Med. **178**:663-669, 1936.

29. Diem.[23a] Abel.[16d]

30. (*a*) Lindquist.[12b] (*b*) Ylppö.[15a] (*c*) Braestrup, P. W.: Studies of Latent Scurvy in Infants: I. Capillary Resistance of Newly Born Children and During the First Year of Life, Acta pædiat. **19**:320-327, 1937. (*d*) Lindquist, N.: Das Verhalten der Gefässprödigkeit im Kindesalter, ibid. (Supp. 1) **17**:247-260, 1935. (*e*) Beintker, C.: Über das Endothelsymptom im Säuglingsalter, Ztschr. Kinderh. **37**:225-235, 1924.

course. Newborn term infants were studied daily by Bayer [31] and Maloney,[32] who found at birth a low capillary resistance, which rose rapidly in the first week to the highest level attained in life. The "critical resistance" at this time is above 50 cm. over all parts of the body.[33] The skin of the infant is resilient, and the blood vessels are situated deep in the dermis, with the result that they are not easily accessible to injury. When this deep network of vessels begins to project capillaries into the newly forming papillae at about 3 months of age, the capillary resistance begins to fall.[34] The results of stasis tests in babies and children are less clear and definite but are in general agreement with those of the suction tests. [30c] The capillary resistance declines in childhood rather rapidly, so that adult levels are reached by the age of 12 years [35] (Table 5). In the adult it is unchanged by age until a gradual decline begins after the age of 50 or 60 years.[36] The capillary resistance of women is slightly lower than that of men.[37]

Anatomic Factors.—Skin Color: Blonds have a slightly lower capillary resistance than brunets, and, of course, the tests cannot be used on persons whose

TABLE 5.—*Capillary Resistance in Childhood*

	Capillary Resistance, Cm. Hg			
	Infraclavicular Space		Antecubital Space	
Age Range	CR	S. D.*	CR	S. D.*
1- 3 mo.	38	10	35	12
1- 2 yr.	20	8	34	8
3- 6 yr.	12	4	33	8
11-13 yr.	10	4	26	9

* Standard deviation.

These are median values by "critical resistance" negative-pressure method. Note the standard deviation is large. The antecubital space is dependent relative to the infraclavicular space. Adapted from data of Brock and Malcus.[34]

31. Bayer.[22a] Bayer.[28b]

32. Maloney, W. C.: The Occurrence of Abnormal Capillary Fragility in the Newborn, Am. J. M. Sc. **205**:229-233, 1943.

33. (*a*) Lindquist.[12b] (*b*) Lindquist.[30d] (*c*) Brown, E. E.: Capillary Resistance in Scarlet Fever, Arch. Pediat. **57**:553-562, 1940. (*d*) Abt, A. F.; Farmer, C. J., and Epstein, I. M.: Normal Cevitamic (Ascorbic) Acid Determinations in Blood Plasma and Their Relationship to Capillary Resistance, J. Pediat. **8**:1-19, 1936.

34. Brock, J., and Malcus, A.: Über die Capillarresistenz im Kindesalter: Systematische Untersuchungen des Rumpel-Leede sowie der Saugglockenwirkung auf Brust und Arm, Ztschr. Kinderh. **56**:237-252, 1934.

35. Hecht.[1] Lindquist.[12b] Lindquist.[30d] Brown.[33c] Abt and others.[33d]

36. (*a*) Tey.[13] (*b*) Dalldorf, G.: Sensitive Test for Subclinical Scurvy in Man, Am. J. Dis. Child. **46**:794-802 (Oct.) 1933. (*c*) Anderson, G. K.; Hawley, E. E., and Stephens, D. J.: Capillary Fragility and Vitamin C, Proc. Soc. Exper. Biol. & Med. **34**:778-782, 1936. (*d*) Holmgren, I., and Lyttkens, H.: Étude sur la fragilité capillaire, Acta med. scandinav. **80**:575-587, 1933.

37. (*a*) Diem.[23a] (*b*) von Borbely, F.: Über die Blutungsbereitshaft der Haut, München. med. Wchnschr. **77**:886-888, 1930. (*c*) Rudel, I.: Die Capillarresistenz und ihre Beziehungen zur Menstruation bei der Frau, Klin. Wchnschr. **20**:226, 1941.

epidermis is so deeply pigmented that the petechiae cannot be seen. Anemic persons may form petechiae too pale to be seen.[38]

Skin Structure: The effects of the structure of the skin on the determination of the capillary resistance are difficult to assess. They are of greater importance in the suction than in the stasis tests. Though the thickness and stiffness of the epidermis are known to influence the results of the tests, their practical importance is doubtful when the test areas chosen are protected from trauma and the elements.[39] The importance of the effects of subcutaneous fat and the looseness of the skin is unsettled.[40] When turgor and tissue pressure are increased by edema, there is a considerable rise in capillary resistance, but when they are decreased by dehydration there is no diminution of the capillary resistance.[41] Experiments with suction to determine the effect on the capillaries of stretching per se suggested that the effect is not important for those capillaries in the center of the suction cup.[42]

Vascular Structure: The blood vessels are composed of endothelium and several concentric sleeves of supportive tissues. The results of the capillary resistance tests are probably influenced more by the strength of the supporting tissues than by that of the endothelium itself. Histological study of suction-induced petechiae in normal skin has shown fragmentation of the elastic fibers in the vicinity of the hemorrhage without evidence of damage to the endothelium. Blood cells may escape by diapedesis through the widened intercellular spaces, with immediate resumption of the normal shape and function of the vessel. Actual rhexis may occur only in the abnormal skin.[43] The question of the site of the extravasation has not been settled, although histological and biomicroscopical data suggest several possible sites in the normal and the abnormal skin: the smaller arterioles,[44] the arteriolar-capillary junction,[45] the capillary loops,[46] and the smaller venules.[47]

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38. (*a*) Diem.[28a] (*b*) Schweppe, J.; Lindberg, H. A., and Barker, M. H.: Experience with 3 Vascular Fragility Tests in Hypertension, Am. Heart J. **35**:393-402, 1948. (*c*) Molitch, M.: Subclinical Scurvy in Children: Application of Capillary Resistance Test, J. Lab. & Clin. Med. **21**:43-49, 1935.

39. Lindquist.[12b] Abel. [16d]

40. (*a*) Hecht.[1] (*b*) Footnote 11 *d* and *e*. (*c*) Lindquist.[12d] (*d*) Sack.[14] (*e*) Sack.[16b] (*f*) Hein, H.: Die Capillarresistenzverminderung bei Hypertension und der Versuch einer Behandlung mit Rutin, Klin. Wchnschr. **26**:466-469, 1948. (*g*) Tenconi, A.: La così detta "fragilità capillare" nell'età infantile, Pediatrica **37**:1072-1092, 1929.

41. Lindquist.[12b] Tocantins, L. M.: Functional Changes in the Skin in Experimental Purpura, Arch. Dermat. & Syph. **34**:459-464 (Sept.) 1936.

42. Bexelius.[8] Wiemer.[11d] Lindquist.[12b] Zahorski.[15b]

43. (*a*) Peck, S. M.; Rosenthal, N., and Erf, L.: Purpura: Classification and Treatment with Special Reference to Treatment with Snake Venom, Arch. Dermat. & Syph. **35**:831-867 (May) 1937. (*b*) Bennecke: Zur Bestätigung des Rumpel-Leedeschen Phänomens bei Scharlach, München. med. Wchnschr. **58**:740, 1911. (*c*) Ruedemann, A. D.: Conjunctival Vessels, J. A. M. A. **101**:1477-1481 (Nov. 4) 1933.

44. (*a*) Lindquist.[12b] (*b*) Rossman, P. I.: Capillary Resistance in Artificially Induced Fever, Ann. Int. Med. **14**:281-287, 1940.

45. Muller, O.: Die feinsten Blutgefässe des Menschen, Stuttgart, Ferdinand Enke, 1937. Humble, J. G.: Mechanism of Petechial Hemorrhage Formation, Blood **4**:69-75, 1949.

46. Hecht.[1] Lindquist.[12b] Bennecke.[43b] Davis, E.: Capillary Microscopy with Special Reference to Capillary Petechiae, Am. J. M. Sc. **212**:192-196, 1946. Reid, J.: Personal communication to the authors, 1949.

47. (*a*) Hecht.[1] (*b*) Lindquist.[12b] (*c*) Dalla Torre, G., and Dusso, R.: La determinazione della resistenza capillare, Riv. clin. med. **34**:620-626, 1933. (*d*) Lee, R. E., and Lee, N. Z.: The Peripheral Vascular System and Its Reactions in Scurvy: Experimental Study, Am. J. Physiol. **149**:465-475, 1947.

The anatomy of the blood vessels is quite variable over the surface of the body. The anteromedial surfaces of the extremities are thickly supplied with fragile blood vessels, in contrast to the rarity and toughness of the vessels on the posterolateral surfaces, thus accounting for the low capillary resistance in the antecubital space and the high capillary resistance on the side and back of the arm. This region was carefully studied by Dalla Torre and Dusso, who found that a deviation of a few centimeters caused a great change in capillary resistance, although corresponding areas of the two arms gave identical values, as did the same areas when retested.[47c] The fact that the extremities and head present no large areas wherein the structure and distribution of the cutaneous vessels are uniform explains many unsatisfactory experiences with capillary resistance determinations.

Hecht's observation that the capillary resistance is high in all dependent areas of the body has been confirmed by many investigators.[48] He noted that the uniformly high capillary resistance of the newborn infant diminishes over the upper portions of the body as the child grows older but remains high in the dependent portions. He suggested that the walls of the blood vessels of the dependent areas acquire strength

TABLE 6.—*Capillary Resistance of Normal Male Adults*

Body Area Tested	CR, Cm. Hg	
	CR	S.D.*
Forearm, medial aspect	22	4
Forearm, lateral aspect	38	12
Infraclavicular space	20	6
Epigastrium	24	3
Gluteal region	32	8
Thigh, medial aspect	30	10
Thigh, lateral aspect	48	15

* Standard deviation.

These are average values by "critical resistance" negative-pressure method. Note the higher capillary resistance (CR) of the dependent areas and the lateral aspects of the extremities. Again the standard deviation is large. Adapted from the data of von Borbely.[37b]

from the stimulus of the raised venous pressure subsequent to the adoption of the erect posture. His belief was encouraged by the finding that the capillary resistance of persons with chronic venous hypertension secondary to valvular heart disease was higher than the normal over all parts of the body. His theory is generally accepted. These differences over the surface of the body are illustrated in Tables 5 and 6. Franke compared the capillary resistances of several parts of the body and found that they bore certain average ratios to one another but with wide individual differences.[49] It has been suggested that a more representative capillary resistance value might be obtained by examining several body regions at each testing.[50]

The capillary resistance of the buccal membranes has been found to be slightly higher than that of the inner surface of the arm.[16d] Measurement of the capillary

48. (*a*) Wiemer.[11d] (*b*) Sack.[16b] (*c*) Diem.[23a] (*d*) Lindquist.[30d] (*e*) von Borbely.[37b] (*f*) Mengler, O.: Die Prüfung der mechanischen Capillarresistenz der Haut bei hämorrhagischen Diathesen, Klin. Wchnschr. **9**:1301-1302, 1930.

49. Franke, H.: Die Veränderung der Capillarfestigkeit der Haut als reflektorisches Krankheitszeichen innerer Organe, Ztschr. klin. Med. **138**:620-634, 1940.

50. Guiffre, M.: Das Verhalten der Capillaren und Thrombocyten bei kindlicher Tuberkulose, besonders bei Erscheinungen von Purpura, Ztschr. Kinderh. **47**:177, 1929.

resistance of the colonic mucosa has been attempted in patients with colostomy openings.[51]

Physiologic Factors.—Physiologic factors are concerned with the tone and degree of filling of the cutaneous vessels. Changes occur constantly in response to nervous and humoral stimuli. Vascular resistance varies inversely with distention, which, in turn, is largely controlled by the tone of the arteriolar-capillary sphincters.

Koller and Diem injected small amounts of isotonic sodium chloride solution and other substances intradermally and consistently found a rise of the capillary resistance for several hours.[52] This action they attributed to the effects of the cutaneous pain. Pain referred to skin areas from disorders of internal organs, however, has been found to lower capillary resistance in the area of reference.[49] The vasomotor activity in anxiety is said to raise the capillary resistance of the skin considerably while lowering that of the colonic mucosa.[51] Da Silva-Mello noted that capillary resistance determinations made on a subject when he is emotionally disturbed are higher than those made when he is calm.[53] Fatigue has been found to lower the capillary resistance somewhat.[54] Insulin-induced hypoglycemia produces a marked fragility which can be prevented by the use of sedatives, supposedly through their effects on the vegetative nervous system. Hyperglycemia was without effect.[55] A marked rise in capillary resistance occurs within four hours after administration of corticotrophin (ACTH) to persons with capillary resistance depressed by illness. The effect was ascribed to increased adrenal-cortical secretion.[56]

Operations and injuries are accompanied with a great rise in capillary resistance lasting several days.[57] Robson warns that the rise in capillary resistance with splenectomy may be nonspecific.[58] Ungar noted a rise in capillary resistance in injured guinea pigs which lasted as long as eight days and was transferable from the injured to a normal pig by transfusion.[59] Scarborough noted a capillary resistance rise after transfusions in human subjects and after injection of blood or plasma into the tissues or gastrointestinal tract.[60] He has no explanation for this observation which could not be confirmed by Koller and Diem.

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51. Grace, W. J.; Wolf, S., and Wolff, H.: Life Situations, Emotions, and Chronic Ulcerative Colitis, J. A. M. A. **142**:1044-1049 (April 8) 1950.

52. (*a*) Diem.[23a] (*b*) Koller, F., and Diem, E.: Die Beeinflussung der Kapillar-Resistenz durch exogene und endogene Faktoren, Schweiz. med. Wchnschr. **75**:753-757, 1945.

53. (*a*) Dalla Torre and Dusso.[47c] da Silva-Mello, A.: (*b*) Die Wandresistenz der Blutkapillaren: Eine einfache, klinische Methode zu ihrer genauen Messung, München. med. Wchnschr. **76**:1717-1718, 1929; (*c*) Recherches sur la résistance des capillaires sanguins, J. physiol. et path. gén. **28**:377-386, 1930.

54. Bexelius.[8] Diem.[23a]

55. (*a*) Holland.[27] (*b*) Bartelheimer, H., and Baehrecke, H.: Die Capillardichte in der Hypoglykämie, Ztschr. ges. exper. Med. **114**:408, 1945.

56. Robson, H. N., and Durhie, J. J. R.: Capillary Resistance and Adrenocortical Activity, Brit. M. J. **2**:971, 1950.

57. Koller and Diem.[52b] Scarborough, H.: The Effect of Surgical Operation upon Capillary Resistance, Edinburgh M. J. **51**:335-338, 1944. Lexer, E. W.: Der Capillartest für das Vitamin P und seine Anwendung in der Klinik, Deutsche Ztschr. Chir. **253**:602-620, 1940.

58. Robson, H. N.: Idiopathic Thrombocytic Purpura, Quart. J. Med. **18**:279-297, 1949.

59. Ungar, G.: Effect of Trauma on Bleeding Time and Capillary Resistance, J. Physiol. **103**:18P, 1944.

60. Scarborough, H.: (*a*) Footnote *22d*; (*b*) Studies on Stored Blood: Effect of Transfusion on Capillary Resistance, Edinburgh M. J. **48**:555-560, 1941; (*c*) Vitamin P: Observations on the Capillary Resistance in 2 Cases of Scurvy, ibid. **51**:381-387, 1944.

The effect of the blood pressure on the capillary resistance was studied by Tey, who believed it necessary to use a suction directly proportional to the blood pressure to which the blood vessels of the subject have become adapted.[13] His opinion is shared by most workers using stasis methods. However, while there is evidence that capillary resistance is directly proportional to capillary pressure,[61] there are many who doubt that the individualizing of the test according to blood pressure is either useful or desirable.[62] Lewis and Harmer have pointed out that one can only guess at the actual pressure, either positive or negative, which one exerts on the blood vessels of the skin.[63]

Heat applied to an area of skin causes a local vascular fragility, and heat applied to the whole body causes a generalized fragility. Chilling causes a rise in the capillary resistance. These effects disappear soon after the temperature of the skin returns to normal.[64]

The menses are attended by a 10 to 20% drop in the capillary resistance, beginning several days prior to the onset and returning to normal before cessation of the flow.[65] The menopause is said to be accompanied with vascular fragility.[66] These phenomena have been attributed to hormonal and neurovascular imbalances.

Many have noted a marked rise in capillary resistance from the cutaneous vasoconstriction caused by administration of epinephrine,[67] posterior-pituitary extracts, and ergotamine.[52] Histamine in flushing doses lowers the capillary resistance dramatically in a few minutes, with a subsequent rise in an hour to excessively high

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61. Salvioli, G.: Neue Richtungen im Studium der Kapillargefässe am lebenden Objekt, München. med. Wchnschr. **80**:937-941, 1933.

62. (*a*) Bexelius.[8] (*b*) Wiemer.[11d] (*c*) Hein.[40f] (*d*) Beaser, S. B.; Rudy, A., and Seligman, A. M.: Capillary Fragility in Relation to Diabetes Mellitus, Hypertension, and Age, Arch. Int. Med. **73**:18-22 (Jan.) 1944. (*e*) Munro, H. N.: Personal communication to the authors, 1949.

63. Lewis, T., and Harmer, I. M.: Observations upon the Rupture of Minute Vessels in the Skin and upon the Distribution of Cutaneous Hemorrhages and Other Skin Eruptions, Heart **13**:337-355, 1926.

64. (*a*) Bexelius.[8] (*b*) Rossman.[44b] (*c*) Walterhöfer, G.: Experimentelle Untersuchungen über das Endothelsymptom, München. med. Wchnschr. **72**:1819-1821, 1925. (*d*) Gabbe, E., and Krichberg: Beobachtungen über die Resistenz der Hautkapillaren, Zentralbl. inn. Med. **57**:864-866, 1936.

65. (*a*) Brown.[33e] (*b*) Rudel.[37e] (*c*) Tey, A., and Marhuenda, P.: Sobre las modificaciones de la fragilidad capilar normal humana durante el ciclo menstrual, Prensa méd. argent. **32**:2505-2516, 1945. (*d*) Brown, E. E., and Wasson, V. P.: Capillary Fragility and Menses in Rheumatic Girls, J. Pediat. **30**:455-458, 1947. (*e*) Seyderhelm, R., and Heinemann, M.: Die Bedeutung des Endothelsymptoms für die Diagnostik und Therapie endokriner Störungen, insbesondere der ovariellen Insuffizienz, Deutsche med. Wchnschr. **56**:860-863, 1930.

66. Seyderhelm and Heinemann.[65e] Vogt, E.: Zur Theorie und praktischen Verwendbarkeit des Endothelsymptoms, Deutsche med. Wchnschr. **48**:1007, 1922. Bickel, L.: Das Endothelsymptom bei Schwangeren: Bemerkungen zur Arbeit von Louros, Zentralbl. Gynäk. **55**:2428-2430, 1931. Bickel, L.: Kann das Endothelsymptom als Test für Diagnose und Therapie ovarieller Funktionsstörungen angesehen werden? Deutsche med. Wchnschr. **55**:1105-1107, 1931.

67. (*a*) Bartelheimer and Baehrecke.[55b] (*b*) Brewer, G. I.: Rhythmic Changes in the Skin Capillaries and Their Relation to Menstruation, Am. J. Obst. & Gynec. **36**:597-612, 1938. (*c*) Galmiche, P.: La résistance des capillaires et la vitamine de permeabilité, Semaine hôp. Paris **22**:1463-1470, 1946. (*d*) Lewis, T.: The Force Exerted by the Minute Vessels of the Skin in Contracting, Heart **11**:108-117, 1924.

levels.[68] It may be that the release of histamine explains the local drop of capillary resistance noted in various insults to the skin, such as rubbing, scrubbing, bruising, application of irritating substances, and exposure to ultraviolet light to the point of erythema.[69] Several presumably antihistaminic compounds have been found effective in raising the capillary resistance depression noted in allergic disorders, apparently by opposing the action of histamine or by preserving the body's epinephrine.[70] The effect of rutin and of several of the other "vitamin-P" compounds has been attributed to their presumed vasoconstrictive action,[71] particularly of the terminal arterioles,[72] and to their inhibition of the catabolism of epinephrine.[73] It has been suggested that hyaluronidase may effect a lowering of the capillary resistance.[74] Chambers and Zweifach have reported that direct application of the enzyme to capillaries caused the abrupt appearance of microscopic hemorrhages,[75] but Duran-Reynals and Meyer suspected this effect was due to contaminating substances.[76]

In addition to these, there are many drugs and toxic agents which cause fragility by damaging the blood vessels.

Environmental Factors.—Seasonal: Vascular resistance has been observed by many investigators throughout the temperate zone to reach its lowest level in the early spring and its highest in the late summer.[77] Many apparently healthy persons have abnormal capillary resistance in the months of February, March, and April.

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68. (*a*) Diem.[28a] (*b*) Galmiche.[67c] (*c*) Parrot, J.-L.; Galmiche, P. ,and Richet, G.: Action des antagonistes de l'histamine sur la résistance des capillaires, Compt. rend. Soc. biol. **139**:476-478, 1945.

69. Bexelius.[8] Tenconi.[40g] Ungar.[59] Walterhöfer.[64c]

70. Diem.[28a] Koller and Diem.[62b] Parrot and others.[68c] Halpern, B. N.: État actual de la question des antihistaminiques de synthese, Acta allergol. **1**:1-39, 1948.

71. Haley, T. J.; Clark, W. G., and Geissman, T. A.: Studies on "Vitamin P": Topically Applied "Vitamin P" Like Substances on the Mammalian Capillary Bed, Proc. Soc. Exper. Biol. & Med. **65**:202-207, 1947.

72. Fuhrman, F. A., and Crismon, J. M.: Studies on Gangrene Following Cold Injuries: Effect of Rutin and Other Chemical Agents on Course of Experimental Frostbite in Rabbits, J. Clin. Invest. **27**:364-371, 1948.

73. Galmiche.[67c] Lavollay, J.: La fonction vitaminique P: Elévation de la résistance capillaire du cobaye par les inhibiteurs classiques de l'oxydation de l'adrénaline, Compt. rend. Soc. biol. **138**:801-803, 1944. Wilson, R. H.; Martarotti, T. H., and De Eds, F.: Some Pharmacological Properties of Rutin, J. Pharmacol. & Exper. Med. **90**:120-127, 1947.

74. Peck, S. M., and Copley, A.: Diagnosis and Treatment of Skin Manifestations of Capillary Fragility, New England J. Med. **235**:900-906, 1946. Levitt, L. M.; Cholst, M. R.; King, R. S., and Handleman, M. D.: Rutin Therapy for Increased Capillary Fragility and Retinopathy Associated with Diabetes Mellitus, Am. J. M. Sc. **215**:130-135, 1948. Cella, L. J., Jr., and Means, J. A.: Capillary Fragility and the Intercellular Cement Substances, Marquette M. Rev. **13**:67-71, 1948.

75. Chambers, R., and Zweifach, B. W.: Intercellular Cement and Capillary Permeability, Physiol. Rev. **27**:436-463, 1947.

76. Duran-Reynals, F.: Tissue Permeability and the Spreading Factors in Infection, Bact. Rev. **6**:197-252, 1942. Meyer, K.: The Biological Significance of Hyaluronic Acid and Hyaluronidase, Physiol. Rev. **27**:335-359, 1947.

77. Roberts, L. G.; Blair, R., and Bailey, M.: Seasonal Variations in Capillary Resistance of Institutional Children, J. Pediat. **11**:626-646, 1937.

These findings are explained by the lowered vitamin-C intake in the winter months (consult the excellent review by Munro, Lazarus, and Bell [78]), by the diminished exposure to sunshine and intake of vitamin D,[78] and by the increased prevalence of "streptococcic toxins" at this time.[79]

Diurnal: Roberts, Blair, and Bailey regularly found in children an afternoon fall in the capillary resistance as great as 25%.[77]

Atmospheric: The capillary resistance may vary directly as much as 10 to 20% with changes in the barometric pressure.[80] Tanning of the skin has been found to raise the capillary resistance.[81] The capillary resistance varies inversely with the surrounding temperature.[82]

COMMENT

While results of vascular resistance tests apply only to the small blood vessels of the skin, it is assumed that they reflect the condition of the vessels of the whole body. The truth of this assumption is open to grave doubt, since the cutaneous vessels are different from those of the internal organs, both anatomically and physiologically. Low vascular resistance is a phenomenon which may develop in a variety of normal and abnormal situations and certainly is not peculiar to any disease. Nor is it, though frequently treated as such, a disease or syndrome itself, and therapy aimed at "capillary fragility" must be regarded as treatment of a symptom.

The methods of testing are acknowledged to be crude and incapable of differentiating the many abnormalities which result in increased vascular fragility. The inadequacy of the methods used is attested to by their very multiplicity. Indeed, almost every investigator has felt it necessary to introduce his own modifications, great or small, and, as a result, the procedures are so varied that it is almost impossible to compare any two studies directly. The value of many publications has been lessened by the failure of the authors to describe the details of their procedures. Few have adequately studied the normal, and some have chosen for their control subjects not normal persons but hospitalized patients.

The results in the normal and abnormal subject may be affected by a host of anatomic, physiologic, and environmental factors which, at best, can only be partially controlled. The careful analysis of Anderson, Hawley, and Stephens of their determinations in normal subjects revealed a coefficient of variation of approximately 30%, and the authors emphasized that this variation is greater than that found in the majority of anatomic and physiologic characteristics.[36c] Certainly the efforts of Holmgren and Lyttkens,[36d] Monod and Cara,[16e] Sack [16b] and Franke [83] to reduce

78. Weld, C. B.: A Capillary Resistance Test and Its Relations to Vitamins C and D, J. Pediat. **9**:226-233, 1936.

79. Brown and Wasson.[22c] Brown.[33c] Brown and Wasson.[65d]

80. (*a*) Brown and Wasson.[65d] (*b*) Regli, J., and Stamphli, R.: Die Kapillar-Resistenz als objektives Mass für den Wettereinfluss auf den Menschen, Helvet. physiol. et pharmacol. acta **5**:40, 1947. (*c*) Lassner, A.: Chemische Konstitution und therapeutische Wirksamkeit verschiedener Calciumverbindungen, Ztschr. ges. exper. Med. **107**:1-8, 1940.

81. Bexelius.[8] Diem.[23a] Tenconi.[40g]

82. Lagergren, C. G.: Effect of Temperature Changes on the Strength of the Cutaneous Capillaries, Skandinav. Arch. f. Physiol. **65**:76-83, 1932.

83. Franke, H.: Die Wirkung von Vitamin C, Vitamin P und Fruchtsaftkuren auf die Capillarresistenz bei verschiedenen Erkrankungen, Ztschr. klin. Med. **135**:283-315, 1938.

the phenomena of vascular resistance to a formula with the production of a "constant" do not seem warranted in view of the many variables which have been listed here. The capillary resistance may be an individual characteristic not suited for precise comparison between persons.

Despite its many limitations, however, the capillary resistance determination has a demonstrated value in the study of the status of the small blood vessels. When the subject is in physiologic equilibrium, the capillary resistance is nearly constant. Changes of the capillary resistance in the presence of pathological processes then become significant and valuable in following the course of disease, as has been done successfully in a number of studies. The importance of the information gained from these tests requires their continued development.

ACNE NECROTICA

Relation to Acne Necrotica Miliaris and Response to Penicillin and Other Antibiotics

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ACNE NECROTICA miliaris was first described in the American literature by Lane in 1933.[1] He quoted Sabouraud, who first described the disease in 1928[2] as an abortive form of acne necrotica (acne-varioliformis) and the pathological picture as that of acne necrotica. Lane stated that, in his experience, 15 or 20 lesions on the scalp are a large number to find and did not mention finding lesions on the face and back. In 1937 Montgomery[3] reported the clinical and pathological picture of 25 cases and stressed the small size of the primary lesions and their number (12 to 100) and noted the histological resemblance to the early stages of acne necrotica described by Gans.[4] In 24 of the 25 cases, the lesions were confined to the scalp, the single exception being a few scattered vesicopustules in the bearded region. Ormsby[5] described a similar picture under the title "Pustular Perifolliculitis."

Our first case is of unusual interest because of the severity and extensive involvement, and because it demonstrates a probable relation between acne necrotica miliaris and acne necrotica. It is of further interest because of the prolonged remission induced by parenterally administered penicillin after numerous other therapeutic agents failed.

CASE 1.—A telephone repairman, aged 41, was referred to two of us (C. S. and R. F.) in October, 1945, because of an intensely pruritic eruption of the scalp of approximately two years' duration. It began with a few tiny, itching lesions of the scalp which slowly increased in number by the irregular appearance of small groups of lesions preceded by intense itching. Recently similar lesions had appeared on the face and upper back. There had been no response

1. Lane, J. E.: Acne Necrotica Miliaris of the Scalp, Arch. Dermat. & Syph. **28**:10-12 (July) 1933.

2. Sabouraud, R.: Pyodermites et eczémas: Maladies du cuir chevelu IV. Les maladies suppuratives et exsudatives, Paris, Masson & Cie, 1928. Diagnostic et traitement des affections du cuir chevelu, Paris, Masson & Cie, 1932.

3. Montgomery, H.: Acne Necrotica Miliaris of the Scalp, Arch. Dermat. & Syph. **36**:40 (July) 1937.

4. Gans, O.: Histologie der Hautkrankheiten. Die Gewebsveränderungen in der Kranken Haut unter Berücksichtigung ihrer Entstehung und ihres Ablaufs, Berlin, Julius Springer, 1925, vol. 1, pp. 345-347.

5. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin for the Use of Students and Practitioners, ed. 4, Philadelphia, Lea & Febiger, 1934, p. 1210.

to local treatment by various dermatologists, although some temporary improvement followed a single x-ray treatment of the scalp.

Examination revealed that the scalp was studded with numerous pinhead- to match-head-sized, reddish-brown, crusted, necrotic papules with depressed summits. Many appeared at the hairline, many on the bearded region, and several on the interscapular region. A number of lesions on the scalp and back were definitely vesicular, papulovesicular, or vesicopustular. Many were excoriated and crusted. Some had involuted and appeared inactive, leaving depressed, crateriform pinhead- to match-head-sized scars. These scars were larger, being about pea-sized, in the interscapular region. In all, there were several hundred lesions on the scalp, perhaps a hundred or more on the bearded region, and about 30 on the back. A few centrally depressed papules were present on the nasal half of each orbital ridge, and one was noted on the left nasolabial fold. There was little or no associated seborrhea of the scalp.

Over a period of a full year of observation, there were many remissions and exacerbations at irregular intervals. The following therapeutic agents were employed: (1) x-ray therapy—subfractional doses were given to the scalp with temporary improvement and similar doses to

Fig. 1.—Acne necrotica of scalp showing several active, crusted lesions and the pitted, varioliform scars. Note the tendency toward grouping about the scalp margin.

the face and back with similar result; (2) a 1:1,000 mercury-bichloride lotion in 50% alcohol; (3) potassium arsenite solution, five drops three times daily for one month; (4) ultraviolet radiation; (5) three injections of 12 mg. of oxophenarsine hydrochloride (mapharsen®)—following the first injection a remission of two weeks occurred, but the others had no effect; (6) Staphylococcus toxoid, one injection weekly for 10 injections; (7) autogenous vaccine of a nonhemolytic, coagulase-positive Staphylococcus aureus, which was found on culture; (8) tyrothricin ointment and wet dressings; (9) penicillin ointment, 500 units per gram in a water-miscible base; (10) finally, penicillin, 100,000 units in solvecillin® (a penicillin vehicle) daily for six days. Penicillin procaine was not available at the time this patient was treated.

Following many of the above measures there was a short remission followed in a few days by a new group of lesions. Following the course of parenterally administered penicillin therapy, there was a sustained remission lasting five weeks. When the patient was last seen in October, 1946, the vast majority of the lesions were inactive, but there was a recurrence of a few reddish papules on the scalp and frontal hairline.

Examination of a section of a typical necrotic papule on the back was made by Dr. Fred Weidman, who reported that near the center of the section a thick layer of degenerated polymor-

phonuclear leucocytes intermixed with colonies of bacteria and granular detritus indicated crusting. The epidermis immediately underneath exhibited regeneration, and accordingly it may be assumed that a superficial ulcer or erosion preceded the present disease. A long downward extension of the epidermis in this region should be regarded as a part of the regenerative processes—perhaps in connection with the remains of a hair follicle. Elsewhere, a moderate grade of acanthosis remained as the only pathological abnormality in the epidermis.

Fig. 2.—Acne necrotica of interscapular region. Here the lesions were larger, some almost ecthymatous. Several varioliform scars are seen.

In the corium, there were two sets of pathological changes. One appeared to be more or less in relation to the supposed hair follicle. Here, one or two minute foreign-body giant cells were added to the lymphocytic infiltration and supported the idea that a hair follicle was concerned. Thus, it was not uncommon for a foreign-body reaction to be provoked against the remnants of hair shafts which could persist following a destructive folliculitis. The subepidermal region which underlay the crust was highly hemorrhagic and infiltrated with granules of blood pigment, but inasmuch as there was no fibroblastic hyperplasia of note, any ulcerative

processes that may have been present must have been exceedingly superficial (a second section revealed such a superficial ulceration).

The second set of tissue changes consisted in a fairly dense round-cell infiltration which comprised a broad mantle around the blood vessels and hair follicles. The cells in this case comprised no more than the lymphocytes and plasma cells of a nonspecific inflammatory infiltration such as might occur in connection with the ulcer.

The term "ulcer" which is used above is used in the broad sense—namely, the loss of the epidermis. Being so extremely superficial, it might have been the result of excoriation, whether incited by the folliculitis or not. In this particular specimen there was no necrosis, and the lesion was not at all deep. The hemorrhagic zone which appeared immediately below the epidermis nonetheless indicated that the lesion was probably an indolent one. In short, this could have been a very early example of acne necrotica. The involvement of the scalp and back might also point toward this disease.

Differential Diagnosis of Acne Necrotica Miliaris and Acne Necrotica (Acne Varioliformis)

	Acne Necrotica Miliaris	Acne Necrotica (Acne Varioliformis)
Primary lesion	Follicular pinhead-sized vesicles and vesicopustules	Discrete or grouped, indolent, reddish brown papulopustules, pinhead- to pea-sized, with central necrosis
Secondary lesions	Superficial pinhead-sized crusts, erosions and scars	Pinhead- to pea-sized crateriform scars
Sites of predilection	Confined to scalp in almost all cases (95%); rarely bearded regions; 12-100 lesions, usually few	Usually brow and scalp, less commonly nose and cheeks; rarely seborrheic regions; sternal and interscapular regions; very rarely extremities; number usually few, but may be exceedingly numerous—several hundred
Symptoms and course	Intense pruritus; protracted course with recurrence over months and years	Pruritus usually slight or absent; course protracted with recurrence over months and years
Etiology: age, sex, associated dermatoses	Probably a staphylococcal folliculitis; usually middle-aged men; associated seborrhea uncommon	Probably a necrotizing staphylococcal folliculitis; incidence about equal among middle-aged men and women; associated seborrhea the rule
Complications	None	Small patches of cicatricial alopecia may occur
Histology	Superficial ulceration; serosanguineous crusts containing staphylococci; intra-epidermal vesicles; acanthosis and chronic inflammation of hair follicle; lymphocytic infiltrate in cutis; some obliteration of lumens of blood vessels	Begins in upper hair follicles and extends to entire follicle and sebaceous gland; staphylococci often found; small areas of necrosis; blood vessels adjacent to follicle thrombotic; elastic tissue may be destroyed
Response to treatment and prognosis	Tends to improve with ammoniated mercury but recurs	Improves with ammoniated mercury but tends to recur

COMMENT

The absence of seborrhea, the intense itching, the pinhead-sized crusts and vesicles over the scalp, and the tendency to relapse over a period of months and years all speak in favor of acne necrotica miliaris. The presence of lesions at the hairline, on the face, and on the interscapular region, and the tendency for the papules to develop necrotic centers and leave varioliform scars—these speak in favor of acne necrotica. We feel, however, that this is a distinction without a true difference and agree with Sabouraud and Montgomery that acne necrotica miliaris represents an early or abortive form of acne necrotica. This case would seem to present a transition of the one into the other. It seems illogical to present as separate clinical entities two different stages of the same disease. The above table brings out the salient features of both conditions.

It is at once apparent from this table that there are few differences between the two conditions. It is possible that acne necrotica is a stage of acne necrotica miliaris which represents acquired sensitivity to Staphylococcus toxin, with the subsequent formation of necrotic plugs and varioliform scars.

This acquired sensitivity may represent a form of Arthus phenomenon, with Staphylococcus aureus and/or its products as the allergen and the follicular apparatus as the shock tissue. We have attempted to reproduce the lesion in another patient by injecting the organism grown from a culture from the intracutaneous lesion about the hair follicles at the hairline without result. Similar experiments with Staphylococcus toxoid have also been unsuccessful. We have had no opportunity to pursue these studies with varying concentrations of organisms or toxins and varying modes of administration, but we feel that further studies along these lines are in order to clarify the pathological physiology of this disease. Strumia [6] was able to reproduce the lesions of acne necrotica in his patient by the intradermal injection of a mixture of staphylococci and streptococci isolated from his patient's lesions.

We feel that the name acne necrotica is sufficiently descriptive of both conditions, and suggest that all other names be avoided in the interest of rational dermatological nomenclature.

In 1938, Sulzberger [7] reported a case with lesions on the scalp and cheeks with marked improvement following treatment with Staphylococcus toxoid. We were not able to obtain a sustained improvement with a 10-wk. course of toxoid given to our patient.

CASE 2.—A 27-yr.-old married woman, an office clerk, who had an extensive eruption confined for the most part to the margins of the scalp, forehead, nose, and eyebrows for several years was seen by one of us (A. B. L.). During the past year the lesions left scars on healing, whereas previous lesions had not. The eruption consisted of numerous glass pinhead- to pea-sized depressed scars and many crusted papules, removal of which left a depressed scar, or rather an ulceration. There was a mild seborrhea of the scalp, and there were acne and seborrhea oleosa of the face. The clinical diagnosis was acne necrotica, although the possibility of a papulonecrotic tuberculid was considered.

Treatment consisted of 300,000 units of penicillin in oil twice weekly. There was prompt and dramatic improvement. All lesions healed, and no new lesions appeared. While the patient was under penicillin therapy a mild Streptococcus infection of the throat developed which subsided in one week following sulfadiazine therapy. When 300,000 units of penicillin in oil was given once weekly there was a flare-up of the lesions, but they cleared up promptly when injections were given twice weekly. One flare-up occurred during the menstrual period. After more than four months of penicillin therapy she discontinued treatment for one week, and a severe flare-up occurred again. This time she was given sulfapyridine, 1 gm. three times a day, and in two weeks the lesions cleared up completely. After taking sulfapyridine for six weeks a generalized eruption developed which was considered to be a dermatitis medicamentosa from the sulfonamide. Use of penicillin was again resumed in doses of 300,000 units twice weekly, and again a remission occurred.

A pure culture of a hemolytic Staphylococcus aureus was grown. This proved sensitive to as little as 0.001 units of streptomycin per cubic centimeter, but required as much as 8 units of penicillin per cubic centimeter to inhibit growth. In view of this the patient was given 1 gm. streptomycin daily for five days with considerable improvement. When the therapy was dis-

6. Strumia, M. M.: Experimental Acne Varioliformis, Arch. Dermat. & Syph. **10**:702 (Dec.) 1924.

7. Sulzberger, M. B.: Acne Varioliformis Successfully Treated with Staphylococcus Toxoid, Arch. Dermat. & Syph. **38**:122 (July) 1938.

continued for a few days there was again a flare-up of the eruption. She was now given 600,000 units of penicillin procaine once weekly, which kept the eruption under control to date.

Biopsy revealed a picture practically identical with that described by Dr. Fred Weidman under Case 1.

CONCLUSIONS

1. Acne necrotica responds to adequate parenterally administered penicillin therapy, but the therapy must be continued for an indefinite period since a flare-up occurs promptly when it is discontinued.

2. Acne necrotica also responds to sulfapyridine and streptomycin therapy.

3. Trial of aureomycin therapy is now indicated.

4. Acne necrotica miliaris is probably an early or abortive form of acne necrotica (acne varioliformis).

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CUTANEOUS HYPERSENSITIVITY DUE TO BERYLLIUM

A Study of Thirteen Cases

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DERMATITIS caused by beryllium compounds is one of the principal occupational hazards in beryllium-extraction plants. Gelman [1] cited Pack as having observed a papulovesicular dermatitis on the exposed surfaces of workers engaged in the extraction of beryllium. Ulcers resembling those caused by chromates and dichromates occurred on the fingers of these workers. De Nardi [2] reported 202 cases of dermatitis, 131 cases of tracheobronchitis, and 57 cases of pneumonitis from two beryllium-extraction plants near Cleveland during the period from 1940 to Jan. 17, 1950. Of the 202 cases of dermatitis, De Nardi lists 156 as due to beryllium fluoride (BeF_2) and 45 as due to beryllium sulfate ($BeSO_4$).[3] Many of the workers who acquired the dermatitis also acquired conjunctivitis and rhinopharyngitis.

Van Ordstrand and De Nardi and associates [4] observed that the skin and mucous membrane symptoms occurred in about 25% of the new employees exposed to fumes and dust of inorganic beryllium compounds, principally BeF_2 and $BeSO_4$. The dermatitis was usually confined to the exposed surfaces and varied from diffuse papules and vesiculopapules to macules and patches of edematous dermatitis, with or without visible vesiculation. In many patients crusted inflammatory papules and small ulcerations were located on the hands and wrists. The conjuctivitis consisted of red spots of congestion 3 to 4 mm. in size to involvement of the entire conjuctiva, particularly the lower lid. Dermatitis of the lids was usually concomitant with conjunctivitis. The rhinitis and pharyngitis were diffuse,

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Read at the American Academy of Dermatology and Syphilology, in a Symposium on Industrial Dermatoses, Dec. 5, 1950.

1. Gelman, I.: Poisoning by Vapors of Beryllium Oxyfluoride, J. Indust. Hyg. & Toxicol. **18**:371 (Sept.) 1936.

2. De Nardi, J. M.: Clinical Report of Illness in Ohio Extraction Plants, in Symposium on Current Knowledge of Disease Encountered in the Handling of Beryllium and Its Compounds: Clinical, Pathologic, Experimental and Engineering Data, United States Atomic Energy Commission, Beryllium Advisory Committee, Division of Biology and Medicine, Massachusetts Institute of Technology, January 18, 1950.

3. Hereinafter the names of the compounds when first mentioned will be written and subsequently only the symbols will be given.

4. Van Ordstrand, H. S.; Hughes, R.; De Nardi, J. M., and Carmody, M. G.: Beryllium Poisoning, J. A. M. A. **129**:1084 (Dec. 15) 1945. De Nardi, J. M.; Van Ordstrand, H. S., and Carmody, M. G.: Acute Dermatitis and Pneumonitis in Beryllium Workers: Review of 406 Cases in 8 Year Period with Follow-Up on Recoveries, Ohio M. J. **45**:567 (June) 1949.

TABLE 1.—*Summary of Clinical Course in Thirteen Cases of Dermatitis Caused by Beryllium Compounds* *

Case	Age	Occupation	Chemical Exposure	I. P., Days †	Sites of Dermatitis	Conjunctivitis and Rhinopharyngitis	Duration, Days	Disposition
1	36	Furnace operation	"Melts" BeF_2	14	.....	0	7	Transferred
2	46	Furnace operation	"Melts" BeF_2	14	Face	0	10	Transferred
3	24	Furnace operation	"Melts" BeF_2	7	Neck	+	7	Transferred
4	24	Furnace operation	"Melts" BeF_2	14	Arms	0	7	Transferred
5	22	Furnace operation	"Melts" BeF_2	9	.....	0	15	Recurrence on reexposure
6	21	Furnace operation	"Melts" BeF_2	8	Face, neck, arms, legs, abdomen	+	7	Left employment
7	25	Furnace operation	"Melts" BeF_2	8	Face, neck, arms, chest, palms, buttocks	+	10	Transferred
8	29	Furnace operation	"Melts" BeF_2	9	Face, neck, arms, right knee	+	15	Transferred
9	23	Furnace operation	"Melts" BeF_2	7	Face, neck, arms, chest	+	15	Left employment
10	23	Furnace operation	"Melts" BeF_2	14	.....	+	7	Transferred
11	31	Bottler	Be Powder	14	Face	+	7	Transferred
12	27	Bottler	Be Powder	10	Neck	0	14	Transferred
13	36	Pipe fitter	Drippings from pipes	10	Arms	+	15	Transferred

* All patients were men and white.
† I. P. stands for incubation period.

and the patients complained of an acrid sensation and nosebleeds. Rhinitis and rhinopharyngitis almost invariably preceded the onset of tracheobronchitis and acute pneumonitis.

Because the medical policy of the plants governing employment included careful screening of new employees for allergic and other occupational diseases, Van Ordstrand, De Nardi, and associates [4] were able to determine exactly the time of first exposure and onset of dermatitis. Thus the incubation period was found to vary from three to 10 days. In many workers the dermatitis recurred within

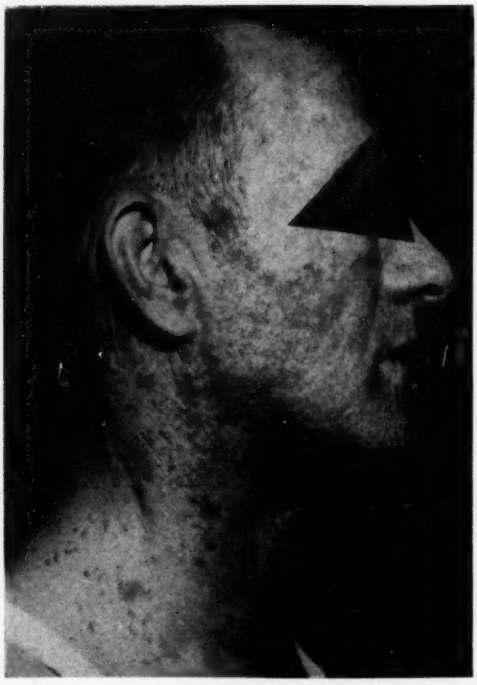

Fig. 1 (case 7).—Dermatitis caused by "melts."

several days after reexposure. These observations led to the belief that the dermatitis, at least, was due to acquired hypersensitivity to beryllium compounds.

Of the 13 patients discussed in this report, the dermatitis was caused by BeF_2 in 10, ground metallic beryllium in two, and water drippings from the surface of overhead pipes coated with dust of various beryllium compounds in one. The 10 patients were exposed to dust from a substance termed "melts," a residue from furnace operations yielding beryllium. It consists of insoluble magnesium fluoride, soluble BeF_2, and pebbles of metallic beryllium. The "melts" is broken up by hand for sublimation in the distillation furnaces. A second exposure to BeF_2 occurs in the removal of the condensers and liners from the distillation furnaces. The dust

formed by breaking up the "melts" and cleaning the liners reaches a high concentration in the immediate atmosphere. The men frequently disregarded the technique of wearing masks, gloves, sleeves rolled down, and collars closed; consequently, the dust is inhaled as well as settling on the skin. BeF_2 and $BeSO_4$ in the dusts are quickly dissolved by sweat and the secretions of the mucous membranes. Conjunctivitis and rhinopharyngitis developed in eight of the 13 patients (Table 1). Occasionally hot particles on striking the skin produced acute inflammatory papules and ulcerations. The two patients were exposed to ground

Fig. 2 (case 7).—Dermatitis of palms and wrists. Note crusted small ulceration near wrists.

beryllium while operating bottling machines. Exposure also occurred while cleaning the machines.

REPORT OF CASES AND SUMMARY OF CLINICAL OBSERVATIONS

The following three cases reported are representative of the group of 13 patients. Two are typical of exposure to "melts" and beryllium powder and the third of accidental exposure to water drippings.

CASE 7 (Figs. 1 and 2).—A white man, aged 26, who had fair clean skin and brown hair and eyes, had a previous industrial history which included four years' experience with chemicals in the form of inorganic solvents and ethylene dichloride with no resultant occupational disease.

The patient began employment as a furnace operator on July 19, 1949. A dermatitis of the exposed surfaces including the face, neck, and upper extremities appeared eight days after initial exposure. The dermatitis consisted of diffuse papules, vesiculopapules, and edematous indefinitely vesicular patches. The papules and vesiculopapules were both perifollicular and interfollicular. On the wrists and dorsa of the hands were several small crusted inflammatory papules and ulcerations. Numerous pale-red maculopapules were evenly distributed over the palmar surfaces of the hands. The eyelids were red and slightly swollen, accompanied by diffuse conjunctivitis.

The patient was transferred to another type of work precluding exposure to "melts" and the dermatitis subsided in about 10 days. After several months, he returned to operation of furnaces, and the dermatitis recurred on the hands and wrists on the third day.

This patient was the only one of the series to consent to having a skin biopsy. A punch specimen of skin was taken from an edematous area of indefinite vesiculation. The dermatitis had been present for four days. There were several small areas of spongiosis of the epidermis. In the areas lymphocytes and a small number of polymorphonuclear leucocytes

TABLE 2.—*Results of Patch Tests in Patients*

All Solutions Buffered to pH 5.0 to 5.5 with $(NH_4)_2\ C_2H_3O_2$

Case No.	BeF_2 Gm. Be/100 Ml.				$BeSO_4$ Gm. Be/100 Ml.			$BeCl_2$ Gm. Be/100 Ml.			$Be(NO_3)_2$ Gm. Be/100 Ml.			Be Metal Powdered	BeO Powder	Be Disk	Control Anions	Acids
	0.38	0.19	0.019	0.0019	0.38	0.19	0.019	0.38	0.19	0.019	0.38	0.19	0.019					
1	4+	4+	1+	0	2+	1+	1+	3+	3+	1+	1+	1+	0	0	0	—	0	—
2	3+	3+	1+	0	1+	1+	0	2+	1+	0	1+	0	0	0	0	0	0	0
3	2+	1+	0	0	1+	0	0	0	0	0	0	0	0	0	0	0	0	0
4	3+	2+	1+	0	1+	0	0	1+	0	0	1+	0	0	0	0	—	0	—
5	3+	3+	1+	0	1+	0	0	0	0	0	0	0	0	0	0	—	0	—
6	3+	3+	2+	1+	—	—	—	—	—	—	—	—	—	0	0	—	—	—
7	3+	2+	1+	0	2+	1+	0	2+	±	0	1+	±	±	1+	0	0	0	0
8	4+	3+	2+	1+	—	—	—	—	—	—	—	—	—	0	0	—	—	—
9	2+	2+	1+	1+	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10	—	3+	2+	0	—	1+	0	—	1+	1+	1+	0	0	0	0	0	0	0
11	—	4+	2+	0	—	2+	1+	—	2+	0	—	3+	1+	1+	0	0	0	—
12	4+	4+	3+	1+	4+	2+	2+	4+	3+	1+	2+	1+	1+	1+	0	0	0	—
13	—	4+	1+	1+	—	1+	0	—	2+	0	—	1+	0	0	0	0	0	0

Capacity to elicit the degree of reaction: $BeF_2 > BeSO_4 = BeCl_2 > Be(NO_3)_2$.
Control anions: $MgCl_2$, $MgSO_4$, NaF, Al_2F_3, NH_4F, $NaNO_3$, and $(NH_4)_2\ C_2H_3O_2$.
Acids: HF, H_2SO_4, and HCl diluted to pH 2.95.
The degree of reaction 4+, 3+, etc., is recorded for the 72-hr. readings in Tables 1 and 2.

had migrated into the epidermis, and liquefaction degeneration was prominent. The edema extended into the subepidermal region, and in one area extravasation of red blood corpuscles occurred. Perivascular edema and a moderately dense perivascular lymphocytic infiltrate extended to the midcorium. There were no intra-epidermal vesicles found in several sections.

The results of patch tests are recorded in Table 2.

CASE 11.—A white man, aged 27, who had a fair complexion and clean skin and no previous history of occupational disease began employment bottling ground-up metallic beryllium. While cleaning the dust pans of the enclosed machinery, beryllium dust settled on the exposed surfaces of his skin. On the 14th day a pruritic dermatitis appeared on the face, neck, forearms, and hands. The dermatitis consisted of pale-red patches, macules, and maculopapules, somewhat urticarial in appearance. There was no visible vesiculation. The patient was relieved from further contact with beryllium, and there were no recurrences. The results of patch tests on this patient are recorded in Table 2.

CASE 13.—A white man, aged 36, began employment on a job contracted by another company dismantling tanks, pipes, and rafters. Water spray and dripping from the tanks, pipes, and rafters fell on the patient's face, neck, and upper extremities. On his 10th day engaged in this

work, an eczematous dermatitis appeared on the exposed surfaces. The eyelids were edematous, and a spotty conjunctivitis was present. The patient was withdrawn from the plant by his company. The results of patch tests are recorded in Table 2.

A summary of the clinical observations in the 13 patients is given in Table 1, which is self-explanatory.

Experiments with patch tests led Fairhall and associates [5] to conclude that the dermatitis in beryllium workers was due to chemical irritation caused by acidity. Positive reactions were obtained in six persons with strong acid solutions of beryllium oxyfluoride in from one to 18 hr. and with $BeSO_4$ in from six to 24 hr. Beryllium oxide (BeO) did not produce any reactions. The authors stated that the redness of the skin was characteristic of the irritant reaction of corresponding mineral acids. However, they did not mention the pH or concentration of the compounds. In contrast to these conclusions and based on the following study, I believe the dermatitis is an allergic eczematous contact type caused by beryllium compounds.

METHODS AND TECHNIQUE

Preliminary patch tests resulted in positive reactions in my first three patients to 2%, 1%, and 0.1% unbuffered solutions of BeF_2 and negative reactions in two control persons. Although these results indicated that the dermatitis was due to hypersensitivity to BeF_2, it seemed necessary to prove as far as possible that beryllium was the sensitizing allergen.

Solutions of BeF_2, $BeSO_4$, $BeCl_2$, and $Be(NO_3)_2$ adjusted to pH 5.0 to 5.5 with ammonium acetate were made up to contain 0.38 gm. Be per 100 ml., 0.19 gm. Be per 100 ml., 0.019 gm. Be per 100 ml., and 0.0019 gm. Be per 100 ml., which was found to be the highest dilution that produced positive reactions. The solutions thus contained the same amount of beryllium as was in the 2%, 1%, 0.1%, and 0.01% solutions of BeF_2. Insoluble beryllium compounds, powdered metallic beryllium, BeO, and small disks of metallic beryllium 1.0 cm. in diameter and 1 mm. thick were moistened for application as patch tests. Solutions of aluminum fluoride (AlF_3), ammonium fluoride (NH_4F), sodium fluoride (NaF), magnesium sulfate ($MgSO_4$), sodium nitrate ($NaNO_3$), and ammonium acetate ($[NH_4]_2C_2H_3O_2$) were made up to contain the same amount of anion as was in the solutions of BeF_2, $BeSO_4$, $BeCl_2$, and $Be(NO_3)_2$ containing 0.38 gm. Be per 100 ml. A few preliminary tests with these compounds produced only negative reactions in few patients and controls; hence it was deemed unnecessary to buffer them. Further patch tests on patients and controls were performed with hydrofluoric acid (HF), sulfuric acid (H_2SO_4), and hydrochloric acid (HCl) diluted to pH 2.95. Nitric acid was omitted from this study as it has been shown that it does not produce a reaction on the skin at pH 3.0.[6] Later in the course of these studies organic salts of beryllium were obtained. Dilutions of beryllium benzenesulfonate ($Be[C_6H_5O_3S]_2$) and beryllium oxalate ($BeC_2O_4.3H_2O$), both water soluble, containing the same amount of beryllium as was in the dilutions of the inorganic salts (BeF_2, $BeSO_4$, $BECl_2$, and $Be[NO_3]_2$) were used. The water-insoluble organic compounds basic beryllium acetate ($BeO.3Be[C_2H_3O_2]_2$), beryllium salicylate ($Be[C_7H_5O_3]_2.H_2O$), and beryllium monostearate in powder form were moistened and applied as patch tests. Since these compounds gave negative reactions in control persons, further control studies with the anions and pH were deemed unnecessary.

In addition to the 13 patients, patch tests were performed on 16 men and women who volunteered as controls and who had never been exposed to beryllium or its compounds. It was not possible to test each of the substances in each patient and control, but the chemicals were tested in the patients as a group and in the controls as a group. When the organic

5. Fairhall, L. T.; Hyslop, F.; Palmes, E. D.; Alford, W. C., and Monaco, R. A.: Toxicology of Beryllium, Nat. Inst. Health Bull. **181**:1, 1943.

6. Markowitz, M.: Practical Survey of Chemistry and Metabolism of the Skin, Philadelphia, The Blakiston Company, 1942, p. 51.

TABLE 3.—*Spontaneous Flare-Up in Eight of Sixteen Control Persons and Result of Subsequent Patch Tests*

			BeF_2 pH 5.0-5.5 Gm. Be/100 Ml.			$BeSO_4$ pH 5.0-5.5 Gm. Be/100 Ml.			$BeCl_2$ pH 5.0-5.5 Gm. Be/100 Ml.			$Be(NO_3)_2$ pH 5.0-5.5 Gm. Be/100 Ml.						$Be(C_6H_5 \cdot O_2S)_2$ Gm. Be/100 Ml.		$Be(C_2O_4 \cdot 3H_2O)$ Gm. Be/100 Ml.		
Control		Time	0.38	0.19	0.019	0.38	0.19	0.019	0.38	0.19	0.019	0.38	0.19	0.019	Control Anions	BeO Powder	Be Powder and Disks	0.38	0.019	0.38	0.019	Acids pH 2.95
1	SFU*	16 days	2+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—	—	0
	SPT†	72 hr.	—	3+	1+	—	1+	1+	—	0	0	0	0	0	0	0	0	—	—	—	—	—
2	SFU	9 days	2+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—	—	—
	SPT	72 hr.	—	4+	2+	—	2+	0	—	2+	0	—	0	0	0	0	0	3+	1+	3+	1+	0
3	SFU	8 days	3+	3+	0	0	0	0	2+	0	0	0	0	0	0	0	0	—	—	—	—	—
	SPT	72 hr.	—	—	2+	—	—	1+	—	—	±	—	0	0	0	0	0	3+	2+	3+	0	0
4	SFU	10 days	2+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—	—	—
	SPT	72 hr.	—	3+	1+	—	1+	0	—	1+	0	0	0	0	0	0	0	2+	1+	1+	1+	0
5	SFU	14 days	2+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—	—	—
	SPT	72 hr.	3+	—	1+	—	—	—	—	—	—	—	—	—	—	—	—	2+	0	2+	0	0
6	SFU	6 days	4+	—	—	1+	—	—	2+	—	—	0	—	—	0	0	0	3+	—	2+	—	0
	SPT	(Refused)																				
7	SFU	16 days	3+	—	—	—	—	—	—	—	—	—	—	—	—	0	0	3+	—	3+	—	0
	SPT	(Refused)																				
8	SFU	7 days	2+	—	—	—	—	—	—	—	—	—	—	—	0	0	0	—	—	—	—	—
	SPT	(Refused)																				

Capacity to sensitize: $BeF_2 > BeCl_2 > BeSO_4 > Be(NO_3)_2$.

* SFU stands for spontaneous flare-up.
† SPT stands for subsequent patch test.

compounds became available, only the group of controls were available for patch-test study. By this time, however, some of the control persons had become sensitive to the inorganic beryllium salts and were therefore suitable substitutes for the patients. All patch tests were applied for 48 hr. Readings were made at the end of 48 and 72 hr., and in almost all instances the positive reactions persisted for more than a week. In Tables 2 and 3 only the 72-hr. readings are recorded.

No attempt was made to determine the concentration at which the soluble compounds would produce primary irritant reactions.

ANALYSIS OF RESULTS

The results of patch tests in patients and controls are shown in Tables 2 and 3. The control metallic salts containing the anions fluoride, sulfate, chloride, and nitrate gave negative reactions in all patients and controls (Tables 2 and 3). This, coupled with negative reactions to the acids HF, H_2SO_4, and HCl, indicated that the anions did not have positive allergenic properties.

Acidity seemed to be eliminated as a factor in producing the dermatitis by three methods of control. First, the acids at pH 2.95 failed to produce reactions in patients or controls; second, the solutions of BeF_2, $BeSO_4$, $BeCl_2$, and $Be(NO_3)_2$ were buffered to pH 5.0 to 5.5, which is within the normal range of sweat [6]; third, on several controls patch tests with unbuffered solutions of these beryllium salts varying in pH from 3.5 to 4.2 also resulted in negative reactions.

Beryllium acetylacetonate, soluble in alcohol, was the only one of the beryllium compounds used in this study that was found to be enough of a primary irritant as to regularly produce bullous reactions in patients and controls in rather high dilution (0.019 gm. Be per 100 ml.) corresponding to 0.1% BeF_2. A comparison between negative reactions to the other organic and inorganic salts of beryllium in the maximum concentrations used in this study in the controls and bullous reactions to the beryllium acetylacetonate seemed to eliminate a possible inherent primary irritant factor, especially of BeF_2 and $BeSO_4$ which are the principal causes of dermatitis among workers in the extraction plants.

Of the 16 controls, hypersensitivity developed in eight (Table 3). Spontaneous flare-ups developed at the test sites of the inorganic salts in from six to 16 days (Fig. 3). In four, the flare-ups appeared only at the test sites of BeF_2; in two, at the test sites of BeF_2 and $BeCl_2$; and in one, at the site of BeF_2, $BeCl_2$, and $BeSO_4$. Subsequently, positive reactions in 48 hr. were obtained to all four beryllium salts in higher dilutions up to eight months later. In one control in whom no spontaneous flare-up occurred after original patch tests, six months later during some experiments with the Urbach-Koenigstein technique a spontaneous flare-up occurred.[7] In two controls spontaneous flare-up to $Be(C_6H_5O_2S)_2$ and $BeC_2O_4 \cdot 3H_2O$ occurred. These two compounds also produced positive reactions in three control persons who were originally sensitized to the inorganic beryllium compounds (Table 3). In addition, weakly positive reactions were obtained to basic beryllium acetate, beryllium monostearate, and beryllium salicylate.[7] In the controls who did not develop sensitivity, only negative reactions to these compounds were obtained. It is conceivable that the cross sensitivity between inorganic salts and organic-acid salts of beryllium can be explained solely

7. Curtis, G. H.: Unpublished data.

by the allergenic capacity of the beryllium ion including the sensitizing ability and specificity. The anions if attached to the beryllium-protein conjugate probably take no part in the antigen-antibody reaction. Furthermore, it is possible that large numbers of the anions react with other elements of the tissue, releasing active beryllium ions to form antigenic hapten conjugates.

Solutions of $BeC_2O_4.3H_2O$ and $BE(C_6H_5O_3S)_2$ containing 0.38 gm. Be per 100 ml. have a pH of 2.7 and 2.4 respectively. In normal control persons no reactions were obtained in 48 hr. Thus the human skin in these experiments tolerated acid

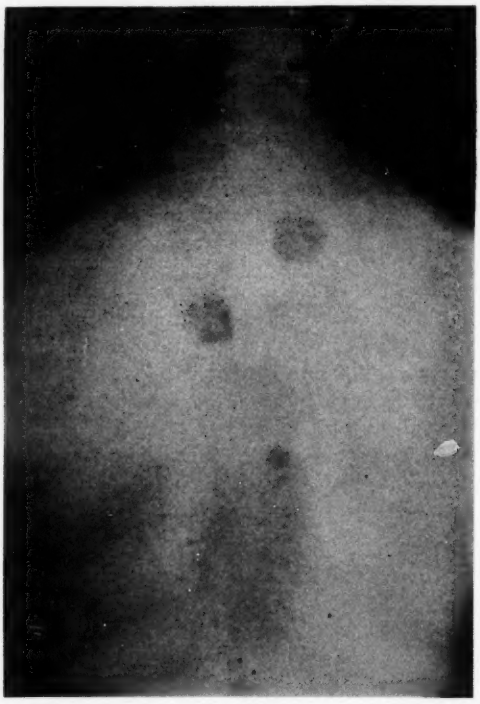

Fig. 3.—Spontaneous flare-up reaction to BeF_2, $BeSO_4$, and $BeCl_2$ in a control person.

solutions of pH 2.4 by the patch-test technique up to 48 hr. This also indicates that the dermatitis is not caused by acidity of the beryllium compounds.

Tables 2 and 3 show interesting phenomena. The four inorganic beryllium salts were selected for this investigation because BeF_2 and $BeSO_4$ were known to cause dermatitis, while $BeCl_2$ and $Be(NO_3)_2$ contain different anions and have not been known to cause dermatitis even among laboratory workers and research chemists who frequently handle them. It is immediately apparent (Table 2) that the results of quantitative patch tests show a variation in the capacity of the compounds to elicit the degree of severity of the reaction. The sequence is $BeF_2 > BeSO_4 =$

$BeCl_2 > Be(NO_3)_2$.[8] This occurred in spite of the fact that corresponding dilutions contained the same amount of beryllium. Although measured amounts of the solutions were not applied to the skin, the small pieces of sheeting of uniform size (0.5 cm. square) used in the patch tests were moistened, and the amount of solution probably did not vary more than 0.01 ml. There seems to be a correlation between this phenomenon and the capacity to sensitize, as is shown in Table 3, in which the sequence is $BeF_2 > BeCl_2 > BeSO_4 > Be(NO_3)_2$. BeF_2 exceeds $BeSO_4$ and $BeCl_2$ in both the capacity to sensitize and the capacity to elicit a greater degree of severity of reaction. $BeSO_4$ and $BeCl_2$ are about equal in this respect, while $Be(NO_3)_2$ under the conditions of this experiment showed little or no capacity to sensitize the skin. I have no explanation for these phenomena, but they are significant in view of the fact that the incidence of dermatitis caused by BeF_2 is almost four times that caused by $BeSO_4$, although a much larger number of workers are employed in the sulfate method of beryllium extraction.[9]

In three patients (Cases 7, 11, and 12, Table 2), ground beryllium metal produced positive reactions. Two of the patients acquired the dermatitis from this form of beryllium. Positive reactions were also produced in these patients by 0.01% BeF_2 (0.0019 gm. Be per 100 ml.). A high degree of sensitivity accounts for the positive reactions to ground beryllium metal of the highest purity which contains from 0.02 to 0.2% BeF_2; thus it is probable that the positive patch-test reactions and dermatitis were produced by BeF_2.

The disks of elemental beryllium and BeO powder elicited only negative reactions in all patients and controls, which may be attributed to the fact that the substances are so extremely insoluble that no hapten-protein conjugate formation is possible. Patch-test sites with other insoluble beryllium compounds such as beryllium dipalmitate and beryllium distearate also showed negative reactions[7] (Tables 2 and 3).

HISTOPATHOLOGICAL OBSERVATIONS OF SPONTANEOUS FLARE-UPS AND PATCH-TEST REACTIONS

The principal pathological features of the spontaneous flare-up consisted of small intra-epidermal vesicles containing fluid and lymphocytes. There were focal areas of intercellular edema and ballooning. In the areas were migratory lymphocytes and a few polymorphonuclear leucocytes. Moderately dense perivascular infiltration of lymphocytes and edema extended into the upper corium (Fig. 4).

Skin specimens from the patch-test sites in both patients and sensitized controls showed tenser reactions than the spontaneous flare-ups. Intradermal vesiculation and spongiosis were more pronounced. Subepidermal edema extended almost the whole length of the reactions and penetrated well up into the rete, producing liquefaction degeneration and, in places, early vesiculation. The larger vesicles contained fluid and numerous leucocytes. The moderately dense perivascular infiltrate consisting of lymphocytes and occasional polymorphonuclear leucocytes and edema extended into the midcorium (Fig. 5).

8. Footnote deleted.

9. Zielinski, J. M.: Personal communication to the author.

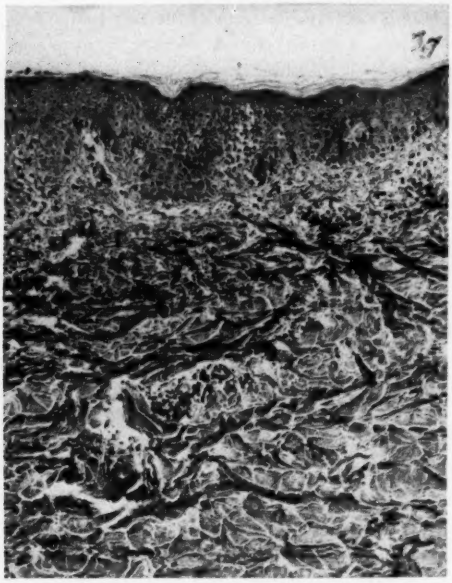

Fig. 4.—Small intradermal vesicle in section from site of spontaneous flare-up (× 100).

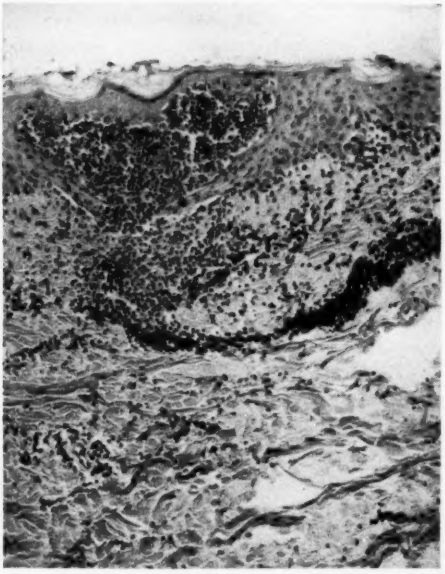

Fig. 5.—Intradermal vesicle containing fluid and leukocytes in section from site of strongly positive reaction to patch test with BeF_2.

COMMENT

Elemental beryllium is insoluble and extremely resistant to strong acids and alkalies. In the presence of moisture, however, it readily forms a coat of the oxide which prevents further oxidation. Beryllium has not been obtained absolutely pure but contains minute amounts of BeF_2 as an impurity. The coat of beryllium oxide also prevents any leaching of the contained BeF_2. This property prevents reaction with sweat and penetration of the epidermis; consequently, it cannot be utilized for purposes of the patch test. If it were so, as in the case of mercury and nickel, a single positive reaction with elemental beryllium in a patient would suffice to prove cutaneous hypersensitivity; therefore, proof of eczematous hypersensitivity to beryllium must be arrived at indirectly by patch tests with beryllium compounds. This indirect approach involves the question of acidity, primary irritancy, and possible antigenic properties of the anions as causes of dermatitis. These factors, I believe, have been eliminated. I assume that the antigenic capacity of beryllium is due to the beryllium ion, while the acidity and anions of the beryllium compounds used in this study serve merely to maintain beryllium in solution and ionic state, thus permitting conjugation with protein and then the hapten-protein antibody reaction.

The positive evidence for proof of hypersensitivity fulfils the clinical, histological, and experimental criteria enumerated by Sulzberger.[10] The clinical evidence obtained in this study includes a source of adequate exposure of persons never previously exposed to beryllium compounds, and an incubation period of seven to 14 days. An eczematous dermatitis occurs which promptly subsides on removal from exposure and recurs on reexposure. Histologically, spongiosis and intraepidermal vesiculation are demonstrated in the dermatitis, spontaneous flare-ups, and positive reactions from patch tests. By the patch-test technique the experimental evidence includes spontaneous flare-ups in persons who had never been exposed to beryllium, the incubation period for the spontaneous flare-up which was found to vary from six to 16 days, subsequent positive reactions obtained in 48 hr. to higher dilutions of the beryllium salts, and positive reactions obtained as long as nine months after the spontaneous flare-up and three years after occurrence of the dermatitis in patients. It is noteworthy that the incubation periods of the dermatitis in patients and spontaneous flare-up in controls practically coincide.

Unfortunately the patients who had mucous-membrane signs refused to cooperate so that it could be determined whether or not the mucous-membrane manifestions were due to hypersensitivity to beryllium compounds. However, this possibility is suggested by the high incidence and concomitant development and course, e. g. exposure, incubation period, signs, and recurrences, along with the dermatitis (Table 1). Similarly, tracheobronchitis and acute pneumonitis follow this pattern although they usually develop at a later time.

The delayed appearance of the manifestations of involvement by the bronchial tree and of acute pneumonitis may possibly be explained by the longer time it takes for the beryllium compounds to reach the epithelium of the lower respiratory tract. Furthermore, in acute pneumonitis the primary site of the pathological

10. Sulzberger, M. B.: Dermatologic Allergy: An Introduction in the Form of a Series of Lectures, Springfield, Ill., Charles C Thomas, Publisher, 1940, Lecture 6.

reaction is the alveolar epithelium.[11] There is additional evidence [7] that allergy may play a role: In a patient who had acute pneumonitis (at the time of this writing) but had never had dermatitis, positive reactions to patch tests were obtained to both organic and inorganic salts of beryllium in high dilution. In another patient who had had acute pneumonitis but no dermatitis, only negative reactions resulted. These two patients are possibly examples of the fact that the skin and mucous membranes may become sensitized independently or simultaneously. Thus it seems possible that sensitivity to beryllium not only develops in the skin but may also develop in the mucous membranes. However, the demonstration by Fairhall and associates [5] of primary or toxic reactions caused by dusts and fumes of beryllium compounds in the lungs of guinea pigs and rats cannot be discounted. These problems need further investigation.

SUMMARY AND CONCLUSIONS

An investigation from the standpoint of allergic eczematous-contact type dermatitis was conducted in 13 cases of dermatitis caused by beryllium compounds among workers in two beryllium-extraction plants near Cleveland. The clinical, histological, and experimental (patch-test technique on human beings) criteria for establishing the dermatitis as an allergic-eczematous type were fulfilled.

Spontaneous flare-ups of eczematous reactions were obtained in eight of 16 control persons who never previously had been exposed to beryllium compounds. The incubation period was found to vary from six to 16 days, which corresponded to seven to 14 days in the clinical dermatitis. Subsequently, 48-hr. eczematous reactions were produced by higher dilutions than the sensitizing concentrations.

Pure beryllium metal is insoluble with respect to the skin and sweat and cannot be used per se for patch test. Therefore anions, acidity, and primary irritancy of the soluble beryllium compounds had to be, and were, eliminated as direct factors in causing clinical dermatitis.

The beryllium ion is believed to be the sensitizing allergen.

Beryllium fluoride possesses the capacity to sensitize the skin to a high degree, which accounts for the high incidence of dermatitis among workers in the fluoride process of beryllium extraction. Beryllium sulfate and beryllium chloride have less capacity than beryllium fluoride to sensitize the skin, while beryllium nitrate was found to have little or no capacity to sensitize the skin, under the conditions of these experiments.

For purposes of patch tests 1% or 2% unbuffered solutions of beryllium fluoride, beryllium sulfate, beryllium chloride, beryllium nitrate, beryllium ammonium fluoride, beryllium oxallate, and beryllium benzenesulfonate are suitable.

It is suggested that mucous-membrane manifestations and possibly acute pneumonitis may be allergic reactions to beryllium compounds.

11. Hazard, J. B.: Pathology of the Acute Disease, in Symposium on Current Knowledge of Disease Encountered in the Handling of Beryllium and Its Compounds: Clinical, Pathologic, Experimental and Engineering Data, United States Atomic Energy Commission, Beryllium Advisory Committee, Division of Biology and Medicine, Massachusetts Institute of Technology, January 18, 1950.

MULTIPLE MILIARY OSTEOMAS OF THE SKIN

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BONE formation in the skin, apart from calcinosis cutis, occurs in several forms: (1) in solitary growths in scars of surgical or other trauma; (2) in ossifying plaques in sclerodermatous diseases; (3) in nevi; (4) in epidermoid carcinomas; (5) in multiple small nodules in children, apparently from embryonic cell rests; (6) in metastatic osteogenic sarcoma, and (7) in miliary nodules in skin damaged by previous pathologic processes. It is with the last type that this report is concerned.

In the cases previously reported, such as those of Hopkins [1] and Leider,[2] acne was apparently the predisposing disease. In other similar cases, such as those of Virchow [3] and Arzt,[4] no such process was noted. Syphilis has been presumed to be a factor in one case [5] in which bone was formed in a chronic leg ulcer, but otherwise this disease has not been reported in predisposition to osteomatosis. We present the case of a patient, similar to those of Virchow, Arzt, Hopkins, and Leider, with multiple miliary osteomas occurring on a face badly scarred by a nodulo-ulcerative late syphilis.

REPORT OF A CASE

H. J., a 46-yr.-old married woman, first entered the University Hospitals on Sept. 12, 1927, because of multiple ulcerations on the anterior scalp, forehead, and cheeks of 18 mo. duration. She stated that she and one brother had had "similar" lesions in the scalp since birth. She gave no history of venereal disease. She was hoarse and had a 1.0-mm. perforation of the hard palate, as well as cigarette-paper scars on the anterior chest, left shoulder, left knee, and left leg. A diagnosis of ulceronodular late syphilis was made, and the otolaryngologist confirmed this with a diagnosis of late syphilitic laryngitis. Subsequently the Wassermann reaction was reported to be strongly positive with both the alcoholic and the cholesterized antigens. Antisyphilitic therapy was begun with administration of potassium iodide and neoarsphenamine, and after six injections of the latter drug the patient was discharged to the care of her home physician with all the ulcers healing nicely. No follow-up study was accomplished.

From the Department of Dermatology and Syphilology, State University of Iowa College of Medicine.

1. Hopkins, J. G.: Multiple Miliary Osteomas of the Skin: Report of a Case, Arch. Dermat. & Syph. **18**:706 (Nov.) 1928. This article contains an excellent bibliography.

2. Leider, M.: Osteoma Cutis: Report of a Case, Arch. Dermat. & Syph. **58**:168 (Aug.) 1948.

3. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1864, Vol. 2, p. 103.

4. Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenberg, 1935, Vol. 2, p. 1028.

5. Meyer, cited by Hopkins.[1]

The patient was not seen again until she reentered the hospital 23 yr. later, on Aug. 24, 1950, in mild cardiac failure from hypertensive cardiovascular disease. Her face, especially the cheeks and forehead, showed widespread depressed thin scars, separated by peculiar reddish-yellow skin which gave the clinical impression of marked sebaceous-gland hypertrophy in a reddened and telangiectatic skin (Fig. 1). Cigarette-paper scars were also noted on the chest, left shoulder, and left knee and leg. There was also scarring in the scalp, and a dimple was noted on the hard palate. Although the record of her previous visit was not available at that time, a tentative diagnosis of late syphilis, probably healed, was made and later confirmed by weakly positive serologic reactions. Because of the peculiar color and texture of the skin, a biopsy was performed; there was no evidence of active late syphilis and no hypertrophy of the sebaceous apparatus. In the mid-dermis, however, were two small rounded masses of bone containing fat. Roentgenographic studies showed multiple small radiopaque nodules with radiolucent centers in the cheeks and forehead (Fig. 2).

Fig. 1.—Scarring of the upper part of the face caused by ulceronodular late syphilis; the multiple small osteomas are not visible.

There was no clinical evidence of active syphilis, and, in view of the patient's age, poor physical condition, and low serologic titer, no further antisyphilitic treatment was given, and she did not wish to have the osteomas treated.

Histopathology.—Microscopic study of the sections (Fig. 3) showed the bony nodules to have the following structure: Around the outside of the bony mass was a fibrous periosteal membrane lying in juxtaposition to dense, compressed, secondary bone. Here the bone was heavily calcified, and the cells were flattened with their long axes tangential to the periphery of the nodule. Centrally there was primary bone, less heavily calcified and not compressed; the cells were rounded, and the spaces around the cells were evident. Along the inner surface of the bone was a layer of flattened, inactive osteoblasts. The center of the nodule was filled with fat, and about the vessels in the marrow fat were a few myeloblastic elements. Several Haversian canals could be made out in the layer of primary bone.

Fig. 2.—The small radiopaque tumors with radiolucent centers in the skin of the forehead demonstrated by soft-tissue roentgenographic technique.

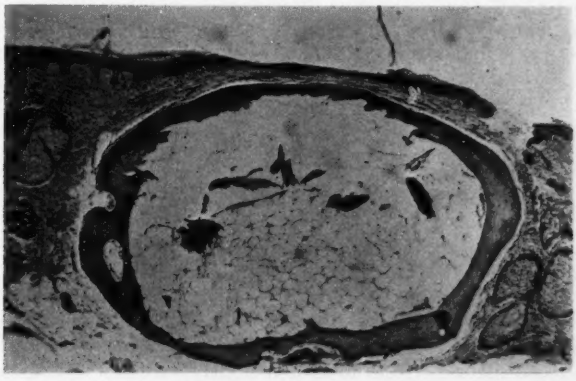

Fig. 3.—Section of skin showing the rounded mass of bone enclosing marrow fat. Two Haversian canals are visible.

COMMENT

Osteomatosis of the skin of the type presented here appears to develop in skin damaged by some scarring process. After the diagnosis had been made by microscopic examination, careful clinical examination of the skin revealed the small hard nodules, particularly by palpation, lying in the peculiarly changed skin between the depressed scars. These nodules showed faintly on the surface as yellowish spots. Neither by inspection nor palpation, nor by x-ray examination were any of these lesions discernible except on the forehead and cheeks. Unlike previously reported cases, there was no history of acne in this patient; her scarring was that of late ulceronodular syphilis. Syphilis as a predisposing factor in multiple miliary osteomas has not been reported so far as we can ascertain.

SUMMARY

The different forms of cutaneous osteomas are listed, and the literature concerning the multiple miliary type is reviewed. A case of this type is reported in which the predisposing factor seems to have been ulceronodular late cutaneous syphilis.

INTRADERMAL LEISHMANIN TEST (MONTENEGRO TEST) IN DIAGNOSIS OF CUTANEOUS LEISHMANIASIS

Report of a Case of Chiclero Ulcer Diagnosed in California

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LEISHMANIASIS is usually divided into two main groups according to the organs primarily involved, namely, visceral and cutaneous leishmaniasis. Visceral leishmaniasis, also known as kala-azar, is caused by a protozoan named Leishmania donovani after its discoverers.

Leishmaniasis affecting the skin is again subdivided into the Old World, or cutaneous, leishmaniasis and the American, or mucocutaneous, leishmaniasis. The Old World leishmaniasis has been given a variety of names, the best-known of which are oriental sore, Dehli button, Aleppo boil and Biskra button. It is endemic in parts of Europe (Sicily, Greece, France, and Spain), Asia (Turkey, Syria, Palestine, Arabia, Persia, Turkestan, India, and China), and Africa (northern part, Abyssinia, and French Congo).

The initial lesion is a papule, often resembling an insect bite. Later an elevated buttonlike nodule of dusky-red color forms. Crusting with or without ulceration develops. The end-result is a depressed radiating scar, making it possible to diagnose leishmaniasis decades after the acute stage. Lesions are often single or occur in small numbers, usually two or three, although several hundred lesions have been counted in some cases. Old World leishmaniasis produces permanent immunity, which is well-illustrated by the fact that the Jews in Bagdad inoculated their children with the serum from lesions on their legs in order to avoid disfiguring scars in the face. Old World leishmaniasis affects, with rare exceptions, only the skin and not the mucous membranes. It is transmitted by personal contact and the bites of sand flies (genus Phlebotomus). Dogs and other domestic animals can act as reservoir. The causative organism is Leishmania tropica, first described in detail by Wright,[1] although observed by others before him.

American, or mucocutaneous, leishmaniasis occurs mainly in Central America, Brazil, Bolivia, Peru, Guiana, and Paraguay. It is much more destructive than the Old World leishmaniasis and is often accompanied by involvement of the mucous membranes. The mucous membrane lesions can result from direct extension of the cutaneous process or can be metastatic, from dissemination of the parasites by way of the lymph or blood stream. The percentage of cases with mucosal involvement varies considerably in different countries. In Brazil there is mucosal involvement in about 20% of the cases, while in Mexico there is practically none. Various names

1. Wright, J. H.: Protozoa in a Case of Tropical Ulcer (Aleppo Boil), J. Cutan. Dis. **2**:1-9 (Jan.) 1904.

are used for American, or mucocutaneous, leishmaniasis, among them *espundia* and *uta* in Peru. In Yucatan and Guatemala leishmaniasis is common among the workers collecting chicle from rubber trees and is known as chiclero ulcer.

In 1909 Lindenberg [2] and Carini and Paranhos [3] found parasites in lesions of leishmaniasis in Brazil, which they identified as belonging to the species L. tropica, the organism causing Old World leishmaniasis. However, in 1911 Vianna in Brazil proposed the name "Leishmania braziliensis" for the parasite he identified in another case of American leishmaniasis, assuming it was different from L. tropica. Since then this name is generally used for the parasite causing American leishmaniasis.[4]

In American, or mucocutaneous, leishmaniasis, sand flies of the genus Phlebotomus are considered to be insect vectors; additional vectors are being suspected, such as Simulium and Acarus in Mexico. The existence of an animal reservoir has not yet been established.[5]

The first case of Old World leishmaniasis diagnosed in the United States was published by Wright.[1] Since then numerous cases of leishmaniasis of the skin have been diagnosed in this country. About 40 have been reported so far, most of them diagnosed by smears or sections, only three by cultures,[6] and apparently none by skin tests. The great majority of cases observed in the United States were cases of Old World leishmaniasis, either in natives of countries where it is endemic or in Americans who visited such countries. Templeton [7] reported a case of the disease in an American woman, who had been inoculated for experimental purposes in Palestine. During World War II, 499 cases of Old World leishmaniasis were observed by Ball and Ryan [8] in the Near East in American Army personnel. Between 1937 and 1948, 12 cases of American cutaneous leishmaniasis were observed in the Panama Canal Zone.[9]

These and similar observations induced several authors rightly to call attention to the possibility that the incidence of leishmaniasis in the United States might be on the increase. The danger of autochthonous cases of leishmaniasis in the United States becomes real if one considers that the vector is present in a number of states. According to Packchanian,[10] six species are present in the United States, and at least

2. Lindenberg, A.: L'ulcère de Bauru ou le bouton d'Orient au Brézil, Bull. Soc. path. exot. **2**:252-254, 1909.

3. Carini, A., and Paranhos, U.: Identification de l'ulcère de Bauru avec le bouton d'Orient, Bull. Soc. path. exot. **2**:255, 1909.

4. Beltran, E.: Parasitology of Mexican Leishmaniasis, secondo curso de dermatologia tropical para medicos, sociedad mexicana de dermatologia, México, D. F., 1948.

5. Goldman, L.: Types of American Cutaneous Leishmaniasis—Dermatological Aspects, Am. J. Trop. Med. **27**:561-584 (Sept.) 1947.

6. (*a*) Packchanian, A.: Leishmaniasis, J. A. M. A. **129**:544-547 (Oct. 20) 1945. (*b*) Forbes, M. A., Jr.: Exogenous Cutaneous Leishmaniasis Proved by Culture, Arch. Dermat. & Syph. **58**:301-307 (Sept.) 1948.

7. Templeton, H. J.: Cutaneous Leishmaniasis Experimentally Produced, California & West. Med. **54**:70-71 (Feb.) 1941.

8. Ball, D., and Ryan, R. C.: Cutaneous Leishmaniasis, Bull. U. S. Army M. Dept. No. 79, pp. 65-73, Aug., 1944.

9. Snow, J. S.; Satulsky, E. M., and Kean, B. H.: American Cutaneous Leishmaniasis, Arch. Dermat. & Syph. **57**:90-101 (Jan.) 1948.

10. Packchanian, A.: The Distribution of Species of Sandflies, Genus Phlebotomus, in the United States and Their Relation to the Transmission of Leishmaniasis, Texas Rep. Biol. & Med. **4**:35-41, 1946.

one of them is found in each of the states of Alabama, California, Georgia, Maryland, North Carolina, and Texas. Packchanian called attention to the possibility of species of Phlebotomus becoming infected in this country from exogenous cases of leishmaniasis and establishing leishmaniasis in the United States with dogs as a reservoir.

With three exceptions, all cases of leishmaniasis of the skin observed in the United States were regarded as exogenous. Benedek [11] reported in 1940 the first case of American cutaneous leishmaniasis acquired in the United States. However, Fox [12] suggested that this patient might have become infected in Poland, and Wenyon, commenting on Benedek's case,[13] and Packchanian [6a] did not think that the organisms were Leishmania. In Gelber's [14] case of Old World leishmaniasis, the disease was diagnosed from sections only. She considered the possibility that it was acquired in the United States, because the only visit to an area where leishmaniasis is endemic had occurred 17 yr. prior to the appearance of the first skin manifestations. A case of autochthonous American leishmaniasis was reported by Stewart, Duncan and Pilcher [15] in Texas. Wenyon, in discussing Stewart's case,[16] stressed the difficulties of making the diagnosis of leishmaniasis from sections alone.

At the present time it is not possible to differentiate L. tropica and L. braziliensis morphologically. In direct smears and in sections the parasites are indistinguishable.[4] Also as far as their cultural characteristics are concerned they seem to be identical. Furthermore, L. tropica and L. braziliensis are again indistinguishable from L. donovani, the causative agent of visceral leishmaniasis, by all available methods of differentiation.

The clinical diagnosis of cutaneous and mucocutaneous leishmaniasis is often difficult even in endemic areas, as these diseases, especially the latter, can simulate one or more of the following diseases: syphilis, yaws, tuberculosis, deep mycoses, leprosy, cutaneous diphtheria, granuloma inguinale, rhinoscleroma, and tropical ulcer.

Present diagnostic methods include examination of smears from the lesion, sections from biopsy material, culture, animal inoculation, agglutination and complement-fixation tests, xenodiagnosis, and skin tests.

Packchanian [6a] considers a diagnosis of leishmaniasis based on the presence of Leishman-Donovan bodies in stained preparations from smears or sections as not conclusive, because yeast-like organisms or other extraneous substances from the lesions may be confused with Leishman-Donovan bodies. He regards culture of L. tropica and L. donovani as essential to establishing the diagnosis. Dostrovsky and Sagher [17] also stress the importance of the culture method for the diagnosis of cutaneous leishmaniasis, asserting that it gives positive results when smears fail.

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11. Benedek, T.: American Leishmaniasis, Arch. Dermat. & Syph. **43**:1093 (June) 1941.

12. Fox, H., in discussion on Benedek.[11]

13. Benedek, T.: American Leishmaniasis, J. Trop. Med. **43**:147 (June) 1940; abstracted in Trop. Dis. Bull. **37**:778 (Nov.) 1940.

14. Gelber, A.: Oriental Sore Possibly Contracted in the United States, Arch. Dermat. & Syph. **46**:739-740 (Nov.) 1942.

15. Stewart, C. D., and Pilcher, J. F.: American Leishmaniasis: Report of an Autochthonous Case, Arch. Dermat. & Syph. **51**:124-128 (Feb.) 1945.

16. Stewart, C. D., and Pilcher, J. F.: American Leishmaniasis, abstracted in Trop. Dis. Bull. **42**:712 (Sept.) 1945.

17. Dostrovsky, A., and Sagher, F.: Diagnostic Significance of the Culture Method in Cutaneous Leishmaniasis (Oriental Sore), Arch. Dermat. & Syph. **54**:543-551 (Nov.) 1946.

While there is no doubt that culture is the most exact method of diagnosis, it presents certain technical difficulties, especially in localities where leishmaniasis is seen only rarely. Contrary to this, it is easy and simple to perform a skin test. This diagnostic method was developed in 1926 by Montenegro [18] and is named after him. He was inspired by E. H. Wagener,[19] who in 1923 reported on a skin reaction in immunized rabbits to extracts from L. tropica and L. infantum. Wagener already noted that this reaction was a group reaction, since extracts from different Leishmania strains gave the same results.

Montenegro used extracts of various strains of Leishmania in cases of leishmaniasis braziliensis and proved this reaction to be specific for leishmaniasis. He also noted that an extract obtained from L. tropica produced an identical reaction in cases of L. braziliensis and used this observation as an argument for the unity of the alleged-different species.

Buss [20] worked with extracts of Leishmania in Brazil and described the histological picture of the positive reaction to a skin test. He attempted to use the skin test to differentiate the various forms of leishmaniasis but came to the conclusion that the skin test, though specific for leishmaniasis, could not be employed as a means of differentiating one form of leishmaniasis from another. Dostrovsky [21] used a vaccine containing killed parasites for an intradermal test in Old World leishmaniasis, which he called L. V. R. (Leishmania vaccine reaction). Sagher [22] employed extensively intradermal vaccine injections prepared with washed flagellates in cases of Old World leishmaniasis and studied the reactions to the vaccine in different dilutions in an effort to differentiate fresh from long-standing infections. According to him, a negative reaction to a skin test in a scar means local cure, while a positive reaction to a skin test in a scar suggests the possibility of a relapse.

While skin tests do not give absolute proof of the cause of any suspected condition, it seems that a positive reaction to the Montenegro test in a patient presenting clinical lesions would give added significance to the findings of Leishmania organisms in smears and sections. A positive reaction to this test indicates that the patient has or has had leishmaniasis. Cutaneous leishmaniasis always heals with scar formation. Therefore it does not seem likely that a positive skin reaction caused by an old leishmaniasis infection, not connected with the disease the patient presents at the time of examination, would interfere with the evaluation.

From the literature available it seems that the skin test has been used only to a minor extent in the diagnosis of leishmaniasis in the United States. This seems unfortunate, since most cases observed in this country were diagnosed only by the findings of Leishmania organisms in smears or sections in addition to the clinical picture. In our opinion, a positive reaction skin would corroborate such findings considerably.

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18. Montenegro, J.: Cutaneous Reaction in Leishmaniasis, Arch. Dermat. & Syph. **13**:187-194 (Feb.) 1926.

19. Wagener, E. H.: A Skin Reaction to Extracts of Leishmania Tropica and Leishmania Infantum, Univ. California Publ., Zoöl. **20**:477, 1923.

20. Buss, G.: Untersuchungen mit Leishmania-Vakzine, Arch. Schiffs- u. Tropen-Hyg. **33**:65-83 (Feb.) 1929.

21. Dostrovsky, A.: The Diagnostic Value of Leishmania Vaccine, Ann. Trop. Med. **29**:123-128 (July) 1935.

22. Sagher, F.: Response of Scars of Cutaneous Leishmaniasis (Oriental Sore) to Injection of Leishmania Tropica Vaccine, Brit. J. Dermat. **59**:205-213 (June) 1947.

The following is a brief report on a case of American leishmaniasis in an El Salvadorian, residing in San Francisco, in which the diagnosis was confirmed by intradermal tests.

REPORT OF CASE

L. M., a 27-yr.-old native of El Salvador noticed a small nodule on his left ear in January, 1948.[23] At that time he had just arrived in El Salvador, returning from Guatemala, where he had been working for seven months in the province of Petén, near the Mexican border, collecting chicle in the jungles. Chicle is a gum obtained from the latex of Sapodilla, largely from Yucatan and Central America, and is used in the United States as the chief ingredient of chewing gum. He was treated for this ear lesion in San Salvador for three months with penicillin, arsenicals and bismuth, but became progressively worse. He arrived in this country in May, 1948. According to his history, his left ear at that time was swollen and ulcerated.

When seen on Dec. 3, 1949, he presented a shallow punched-out ulcer of approximately dime size on the top of the helix of the left ear. The whole upper portion of the ear was swollen and

Fig. 1.—Chiclero ulcer on top of left ear.

infiltrated, and the skin was erythematous (Fig. 1). A punch biopsy specimen was taken from the border of the lesion.

Histopathological Examination.—In one half of the section the epidermis was intact and showed slight hyperkeratosis and some acanthosis. There was a dense infiltrate of histiocytes, interspersed with numerous plasma cells and some lymphocytes in the upper dermis. All through the section there were tuberculoid nodules consisting mainly of epithelioid cells, with a necrotic center and giant cells in the periphery (Fig. 2). Some of these giant cells were of the Langhans', some of the foreign-body, type. In one part of the lesion, to the right of the cartilage, the epidermis was missing. The floor of the ulcer was formed by a fibrinous meshwork containing numerous leucocytes. Below this layer there was a granulation tissue, consisting of numerous histiocytes, plasma cells, lymphocytes, and newly formed blood vessels. In sections stained with Giemsa's stain numerous parasites (leishmaniae) could be seen in histiocytes and giant cells (Fig. 3).

23. Gradow, A., and Fasal, P.: Leishmaniasis Americana (Ear Ulcer of the Chicleros), case presented before the San Francisco Dermatological Society, Jan. 20, 1950.

Laboratory Work.—Results of urinalysis were negative. The hemogram was normal except for evidence of a moderate hypochromic normocytic anemia. The Wassermann reaction on first examination was doubtful and on repeated examinations was negative.

Intradermal tests with 0.1 leishmanin from L. braziliensis [24] led within 24 hr. to a massive swelling and an acute erythematous reaction 7.5 by 5 cm. This reaction increased in intensity for the next 24 hr. and then subsided gradually, being clearly visible for four days.

Fig. 2.—Section from ear lesion. Tuberculoid node with necrotic center and epithelioid cells and giant cells in the periphery; × 70.

Intradermal test with leishmanin from L. tropica [25] led to a similar swelling with acute erythema and a small central vesicle. The erythema measured 6 by 5 cm. after 24 hr., increased in intensity for 24 hr. more, and reached its peak after 72 hr. It subsided gradually and remained visible for five days.

24. Obtained from Dr. Herbert O'Hara in Peru through the courtesy of Dr. Leon Goldman, Cincinnati.

25. Obtained from Dr. Sagher, Jerusalem, through the courtesy of Dr. Leon Goldman, Cincinnati.

Punch biopsy specimens were taken from the center of both positive skin reactions after 72 hr.

Histopathological examination of these specimens gave practically identical pictures: There was massive leucocytic infiltration of the upper corium with prevalence of eosinophilic polymorphonuclear leucocytes. In the deeper parts of the corium, especially around the dilated blood

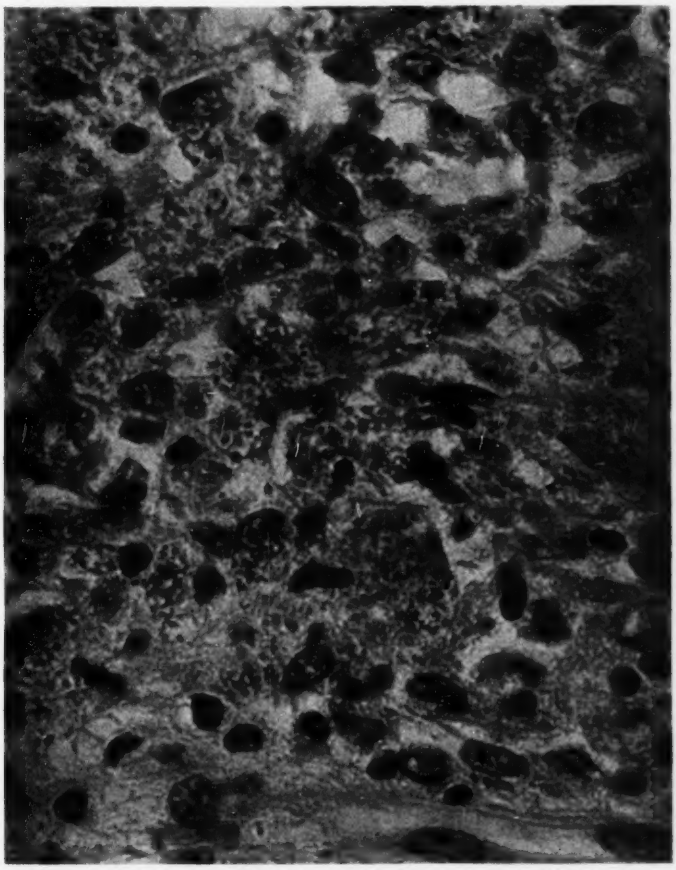

Fig. 3.—Section from ear lesion. Numerous parasites (leishmaniae) can be seen in histiocytes; × 1200.

vessels, there were accumulations of epithelioid cells with some lymphocytes in the periphery, giving the picture of a tuberculoid structure.

The histopathological examination of both skin reactions confirmed the clinical type of the reaction, namely, tuberculoid type.

The patient received intramuscular injections of stibophen (fuadin®), a trivalent antimony preparation. The first injection was 1.5 cc., the second injection was 3.5 cc., and the following injections 5 cc. After the fourth injection the ulcer began to heal, and the infiltrate showed signs

of involution. At present, after 18 injections of stibophen, the only pathological changes visible are a scar on the helix of the left ear and a slight bluish discoloration of the upper part of the ear lobe.

SUMMARY

The intradermal skin test with leishmanin (Montenegro test) is a valuable addition to the various diagnostic methods available for the diagnosis of cutaneous leishmaniasis. It is specific for leishmaniasis and gives a positive reaction if the patient has or has had this disease.

A case of chiclero ulcer (American leishmaniasis) in an El Salvadorian, observed in San Francisco, is reported. The diagnosis was based on the history, clinical findings, detection of the parasites in Giemsa-stained sections, and the positive reaction to the leishmanin skin test.

In this case there were strongly positive reactions to leishmanin from L. braziliensis as well as to leishmanin from L. tropica. This observation gives added emphasis to the close relation, if not identity, of the two organisms.

The leishmanin test cannot be used to differentiate different forms of leishmaniasis.

490 Post St. (Dr. Fasal).

760 Market St. (Dr. Gradow).

COINCIDENT INFECTION OF A HUMAN AND AN ANTHROPOID WITH MICROSPORUM AUDOUINI

Report of a Case

JOHN P. SCULLY, M.D.
READING, PA.
AND
ALBERT M. KLIGMAN, M.D., Ph.D.
PHILADELPHIA

IN JANUARY, 1950, one of us (J. P. S.) was confronted by a patient who stated that she and her pet monkey were scratching pruritic lesions which she thought were ringworm. Considering the number of times that laymen falsely accuse the animal world of conferring infection upon mankind, the piquant fact is that this patient made a correct diagnosis.

REPORT OF CASE

The patient was a 46-yr.-old white woman who operated a pet shop. A week after acquiring a capuchin monkey she noted on the exposed portions of her neck and forearms annular erythematous plaques with a fine branny scale, 0.5 cm. to 1.5 cm. in size. Pruritus was a prominent symptom. Crops of new lesions kept on reappearing during her period of contact with the monkey. The application of 10% salicylanilide ointment to any given lesion was followed by regression within about two weeks.

The simian was a male capuchin approximately 5 mo. old and weighing about 6 lb. (2.7 kg.). He had been trapped in the jungles of Nicaragua and flown from Managua to Miami in a cage next to a honey bear. From there he had been flown to Philadelphia. From the very time of his arrival, he was observed to scratch constantly, and his hair coat was sparse and mangy. The first owner of the monkey and the children in the home where the monkey was kept did not contract ringworm during the month they were exposed to the simian. Lesions appeared on the pet dealer, however, immediately after acquisition of the monkey.

During the few months of ownership by the pet dealer, the animal was harassed by itching, as indicated by violent scratching. There was generalized irregular thinning of the hair with slight scaling of the epiderm. Many of the hairs were broken off. The tail, in particular, had a moth-eaten appearance. There were no discrete, well-defined areas of alopecia such as one sees in human ringworm. The lesions of the monkey showed no tendency to regress after a period of six months.

The pet owner was naturally distressed by the recurrent episodes of ringworm infection which she endured. As a consequence she bequeathed the monkey, with some sentimental misgivings, to Mr. Rebell, an expert mycologist of this department. He in turn had a personal opportunity to study this disease by reason of ringworm lesions developing on the exposed portions of his body. His wife shared this affliction with him. After some familial strife, the monkey was considered dangerous to human society and was finally sacrificed.

Culture.—Numerous cultures of both the pet owner and the monkey yielded the identical organism. This upon study proved to be Microsporum audouini, the organism responsible for

From the Department of Dermatology and Syphilology, University of Pennsylvania School of Medicine (Donald M. Pillsbury, M.D., Director).

epidemic tinea capitis in the United States. This particular isolate was unusual in several respects. In the first place, there was abundant macroconidia formation, a property which was maintained throughout subculturing. Ordinarily, this species fails to develop macroconidia except under specialized nutritional circumstances, and even then they are uncommon.[1] Considering the fact that the macroconidia of M. audouini are usually irregular in size and shape with many abortive forms, the macroconidia of this isolate were often fairly regular in appearance. The walls were quite thick. The macroconidium was divided by thick-walled septa into four to eight cells (Fig. 1A). Occasionally the septa were unevenly disposed in such a way as to produce cells of different size. Sometimes one or more of the cells within a macroconidium was bulged out. Bizarre and atypical forms were seen (Fig. 1B). This feature is characteristic of M. audouini.

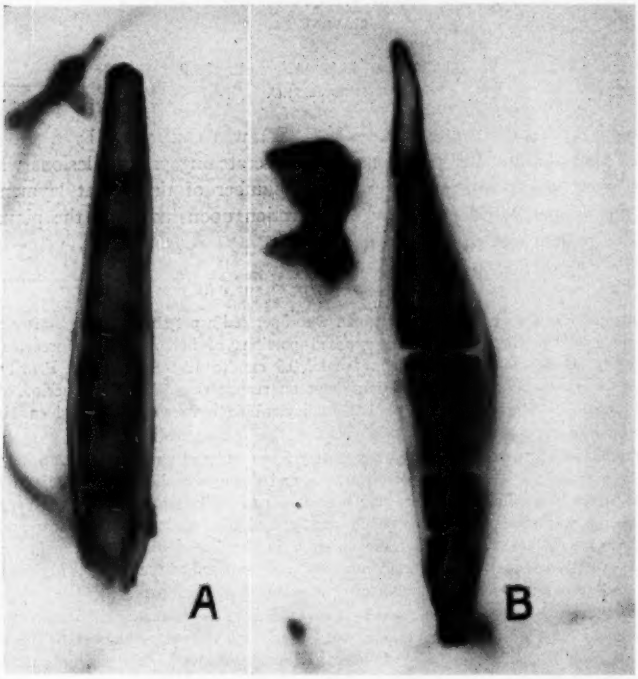

Fig. 1.—*A*, macroconidium (×300). Note thickness of wall. *B*, macroconidium (×300). The irregularity in shape is typical of this species.

The culture grew rapidly, unlike the ordinary isolate of M. audouini. Another unusual feature, usually considered a differential point between M. canis and M. audouini, is that this isolate was able to grow on rice medium. Ordinarily, M. audouini cannot do this, as pointed out by Conant.[2] The ability to grow on rice medium cannot thus be considered a decisive differential point between these two organisms.

1. Hazen, E. L.: Microsporum Audouini: The Effect of Yeast Extract, Thiamine, Pyridoxine and Bacillus Weidmaniensis on the Colony Characteristics and Macroconidial Formation, Mycologia **39**:200-209, 1947.

2. Conant, N. F.: Studies in the Genus Microsporum: Cultural Studies, Arch. Derm. & Syph. **33**:665-683 (April) 1936.

The undersurface of the colony exhibited a rather marked brick-red pigmentation. The colony was white, fairly flat, and tended to show a few radial grooves when mature (Fig. 2).

Fluorescence.—No fluorescence was seen when the monkey was put under Wood's light. However, when the hairs were plucked, the bright, blue-green fluorescence typical of M. audouini infection was observed to occupy about 0.5 mm. at the base of the hair. Evidently, as the hair grew upward out of the follicle the substance responsible for fluorescence deteriorated. The fluorescent material was readily extractable in hot water and corresponded in every way with that observed in human hair.

Biopsy.—A biopsy specimen of the monkey's skin exhibited features which were similar to those observed in scalp ringworm due to M. audouini. The hairs were surrounded by a mosaic of small spores (ectothrix infection). There were no hyphae in the stratum corneum. The inflammatory infiltrate was minimal, a finding which corresponded to the noninflammatory gross characteristics of the lesions.

Fig. 2.—Mature colony on Sabouraud's agar. Note radial grooves at center of growth.

COMMENT

M. audouini is an anthropophilic species, that is, it cannot ordinarily be transmitted to animals. This case is an exception to the general rule that the parasitism of this organism is limited to human beings. Of course, the findings in this case may simply indicate how splendidly similar humans and monkeys are. Perhaps inoculation of various strains of M. audouini into different species of monkeys would show some of the latter to be susceptible. On the other hand, the parasitism of the monkey in this case probably represents a peculiarity in the virulence of the strain rather than an increased susceptibility on the part of the simian. The strain is distinctive culturally and physiologically.

There is a notation in Hull's book, "Diseases Transmitted from Animals to Man,"[3] of a ringworm epidemic in sheep in the Dutch East Indies in 1916. The infection was said to have been contracted from a child with M. audouini var. hemitragi. This report has certain disputable features and may not be valid.

Some interesting questions can be raised in the present situation. Did the monkey contract his infection from human handlers in Nicaragua? Is there an endemic focus of simian ringworm in the Central American jungle just as the scalp infection is endemic among children in certain areas of the United States? The remarkable ease with which the monkey transmitted infection to the various humans in this case suggests a high degree of contagiousness.

SUMMARY

A report of a case of Microsporum audouini ringworm in a capuchin monkey is presented. Several humans contracted the infection from the monkey. The unusual features of the causative organism are described.

150 N. 11th St.

University Hospital.

3. Hull, Thomas G.: Diseases Transmitted from Animals to Man, ed. 3, Springfield, Ill., Charles C Thomas, 1947.

GREEN NAILS

The Role of Candida (Syringospora, Monilia) and Pseudomonas Aeruginosa

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AND
MORRIS D. MARCUS, M.D.
ST. LOUIS

GREEN nails are not commonly encountered in the routine examination of onychomycoses. Usually they are a result of an infection with various species of Aspergillus. These nails have been described as light to dull green with a deep-seated discoloration of the nail plate. Not all green nails, however, are due to aspergillosis. One of us (M. M.) has observed several nail infections in which the causative organism was Candida albicans (Syringospora, Monilia) and in which no other organism could be implicated either by direct examination of the infected

Fig. 1.—Bluish-green nail lesion caused by Candida tropicalis and Pseudomonas aeruginosa.

material or by culture. The infected nails in these cases were light to dull green, with the lesion beginning at the outer margin of the nail and extending into the nail plate.

The observation of an onychomycosis caused by both a yeastlike organism, Candida tropicalis, and Pseudomonas aeruginosa (Bacillus pyocyaneus) throws more light on the etiology of green nails.

B. G., a single white woman, 50 yr. of age, a saleswoman of women's clothing, complained of a bright greenish discoloration of the right thumb nail (Fig. 1).

From the Dermatological Departments of the Barnard Free Skin and Cancer Hospital and the Washington University School of Medicine, service of Richard S. Weiss, M.D.

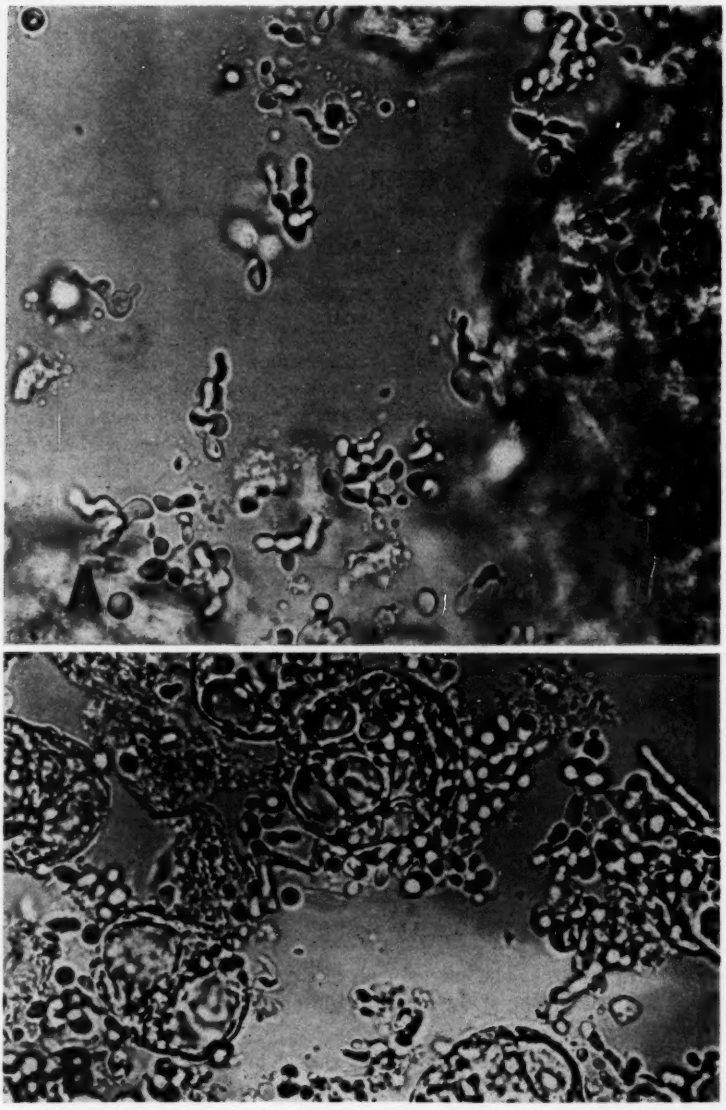


Fig. 2.—Potassium hydroxide preparations of nail scrapings showing simple and multiple budding, ovoid to spherical cells, and bacillary forms; × 890. *A*, preparation made on first visit. *B*, preparation made one week later.

Six months previously the patient bruised her thumb nail, and since that time the nail had not grown in a normal fashion. The green discoloration was noted shortly after the injury. The affected area enlarged gradually and was tender. She had not applied any medication.

Extending from the free margin towards the base of the nail was a fan-shaped area, dark bluish-green in color, involving the nail plate. The nail plate did not appear to be thickened, but the surface of the nail showed ridging, both lateral and longitudinal. The involved area was

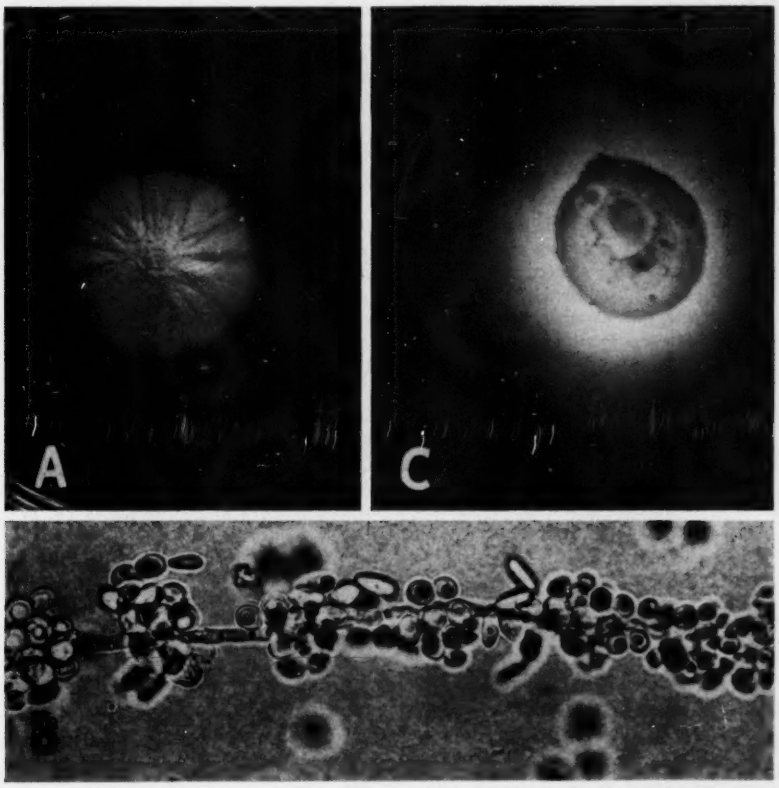


Fig. 3.—*A*, Sabouraud's glucose agar culture of C. tropicalis, 44 days old. *B*, Sabouraud's glucose agar culture preparation of C. tropicalis showing clusters of conidia; × 690. *C*, culture of Pseudomonas aeruginosa on Sabouraud's glucose agar showing fluorescence under Wood's light, 19 days old.

detached from the bed and slightly raised. Between the plate and the bed there was a crumbly caseous material which could be scraped out easily.

Cultures made from the crumbly material yielded two organisms, which were identified as C. tropicalis and Ps. aeruginosa (B. pyocyaneus).

The patient was advised to soak the infected nail in mercury bichloride (1:1,000 in 70% alcohol) twice daily and to apply iodine crystals (2%) in benzene topically. When last seen, the nail had improved considerably.

Biology.—Scrapings were made from the soft, caseous material on the under side of the infected green nail and mounted in 30% potassium hydroxide. This revealed numerous small, ovoid-to-bacillary, simple- or multiple-budding, yeastlike cells and bacilli (Fig. 2). In Gram-stained preparations the yeastlike cells were Gram-positive and the bacilli were Gram-negative.

Several tubes of Sabouraud's glucose agar were inoculated with scrapings and observed for growth. During the course of a few days, yeastlike colonies developed in three of four tubes. In the fourth tube the growth was that of a bacterium. The yeast-like organism was subcultured both in plates (Fig. 3*A*) and in tubes of Sabouraud's glucose agar. On plates the colonies grew out as moist, yeasty colonies, creamy-white in color. As the growth became older and larger small crater-like formations could be seen in the center, possibly ruptured bubbles due to gas formation. The colony became dry and dull and formed fan-shaped sectors. Growth was slow, the colony attaining a diameter of approximately 3.5 cm. after six weeks.

Microscopically the organism produced spherical, ovoid-to-bacillary cells with simple or multiple budding. The hyphae which developed showed verticils of conidia. Conidia also developed along the hyphal wall. Chlamydospores were not noted. The organism was identified as belonging to the genus Candida (Fig. 3*B*).

Subcultures were made in a variety of mediums in an effort to determine the species. In sugar mediums the organism produced acid and gas with glucose, maltose, sucrose, levulose, and galactose, with no effect in mediums containing lactose, arabinose, and inulin. Gelatin was not liquefied. Litmus milk was not acidified or curdled. In broth the organism produced a surface film with numerous bubbles. Chlamydospores were not observed on corn meal agar. The organism was identified as C. tropicalis.

A diagnosis of monilial onychomycosis was made. The green color of the nail, however, was not explained, since it did not conform to any other green-nail condition we had seen. Fortunately, the original cultures were not discarded. Several days later, in the routine examination of the cultures on the work table, it was noted that the bacterial colonies which had developed in the fourth original isolation tube had also grown out in all the isolation tubes. These colonies showed a greenish pigment diffusing into the substratum which was similar in intensity and in color to that of the infected nail. The bacterium was identified as Ps. aeruginosa (B. pyocyaneus). Subcultures were made in plates and later placed under Wood's light, where they showed a distinct greenish-yellow fluorescence (Fig. 3*C*). This is in keeping with Ps. aeruginosa.

As a result of the cultural developments it was concluded that the nail infection was caused by the combined growth of C. tropicalis and Ps. aeruginosa.

COMMENT

Green nails are occasionally observed, and they may be caused by one of several factors. These include discoloration by green dyes, by chemicals, by infection with species of Aspergillus, by invasion by some strains of C. albicans, and, as reported here, by secondary involvement with Ps. aeruginosa.

In general, discoloration by dyes can be easily determined, since the nail involvement is usually superficial without the production of an underlying pathological state. Discoloration by chemicals other than dyes usually reveals puncta in the nail plate, brittleness, striations, and other changes compatible with a chemical dermatitis.

Among the onychomycoses, the Aspergilli are perhaps the best known as producers of green nails. Moore and Weiss [1] reviewed the literature of aspergillotic

1. Moore, M., and Weiss, R. S.: Onychomycosis Caused by Aspergillus Terreus, J. Invest. Dermat. **11**:215 (Sept.) 1948.

onychomycoses and found that 12 species of this genus were capable of producing such a lesion. Bereston, either alone or in association with others,[2] has reported several species as causing green nails, either grayish-green, dull green, or yellowish green. These colors were attributed to the spores in the nail plate. Clinically, the nails were thickened, brittle, with longitudinal striations and usually showed a crumbling of the distal portion of the nail with the presence of a caseous material underneath the nail plate. It is within this cheesy material that the fungi can be demonstrated.

Over a period of several years it has been observed that some cases of onychomycoses have shown a light to dull green color. These cases have been found on culture to be due to C. albicans (Fig. 4). It is a little difficult to explain the greenish discoloration of the nails in these cases of moniliasis. Some strains of C. albicans obtained in culture tend to develop a faint greenish tinge when kept in the stock collection. Ashford, in studying giant colonies of Monilia psilosis (C. albicans), noted six types of growth, of which one was green and honeycombed.[3] One

Fig. 4.—Green nails caused by C. albicans.

could probably speculate on the possibility that there is a recessive tendency to the green color which may be enhanced under certain conditions of growth.

The yeastlike organism C. tropicalis, has been isolated from the sputum of patients suspected of having bronchomycosis, from the vagina, from feces, and occasionally from nail lesions. It is not generally considered to be a very pathogenic organism.

Ps. aeruginosa, commonly called B. pyocyaneus, is a Gram-negative, rod-shaped, motile organism which grows readily on all ordinary culture media and produces a bluish-green pigment (pyocyanin) which diffuses into the medium. Under Wood's light or filtered ultraviolet radiation, the organism and the sur-

2. Bereston, E. S., and Keil, H.: Onychomycosis Due to Aspergillus Flavus, Arch. Dermat. & Syph. **44**:420 (Sept.) 1941. Bereston, E. S., and Waring, W. S.: Onychomycosis and Dermatomycosis Caused by Trichophyton Rubrum and Aspergillus Nidulans, ibid. **52**:162 (Sept.) 1945; Aspergillus Infection of the Nails, ibid. **54**:552 (Nov.) 1946. Bereston, E. S.: Further Studies on Aspergillus Infection of the Nails, South M. J. **43**:489 (June) 1950.

3. Ashford, B. K.: The Etiology of Sprue, Am. J. M. Sc. **154**:157, 1917.

rounding medium through which the pigment has diffused will fluoresce greenish-yellow. This fluorescence is due to fluorescin. Ps. aeruginosa is not considered highly pathogenic for man. It may be found in the human intestine and is often cultured from feces. It is found frequently in cultures made from skin lesions. It has been isolated from numerous conditions in which the evidence pointed to it playing an etiologic role. It has been found in suppurative skin lesions, where blue pus was observed, in corneal ulcers, external otitis, otitis media, infections of the genitourinary and respiratory tracts, in outbreaks of dysentery-like enteric infections, in purulent leptomeningitis, in meningitis following a lumbar puncture or operative exposure of the meninges, in septicemia and endocarditis, puerperal

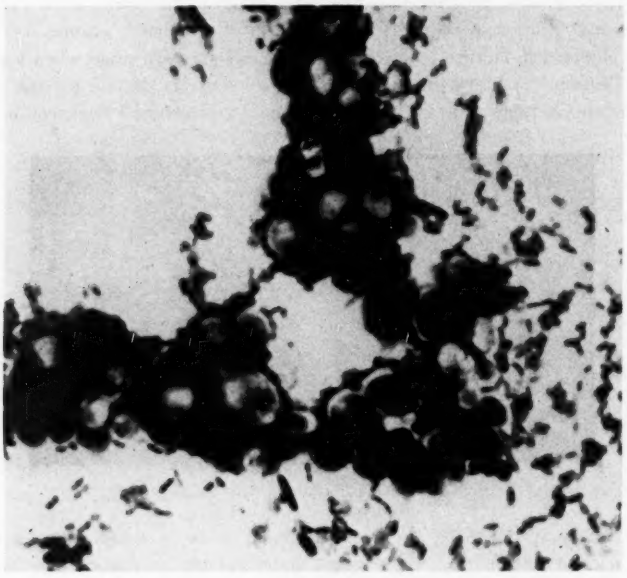


Fig. 5.—Culture smear stained with Löffler's methylene blue solution showing budding yeast-like cells of C. albicans and bacilli of Pseudomonas aeruginosa; × 2,080.

septicemia, and infection of the urinary bladder. The contamination of skin, or, as presented here, nail lesions, should not, therefore, be considered as an extraordinary finding.

Since seeing the patient described here, we have had occasion to examine two additional cases of green nails.

Mrs. M. A., a young housewife, 33 yr. old, the mother of two children, complained of green nails of one month's duration. She stated that her mother had had the same condition six years previously. The patient attributed the green nail condition to the washing at home of the baby diapers. Her mother had washed the diapers of the first child and consequently had developed her infection, whereas the patient herself had been washing the diapers of the second child who was only a few months old.

On examination the infected nails showed varying degrees of intensity of color from a very light green to a more intense green, but did not attain the intensity described in the first case. Longitudinal ridging or striations were not very distinct. Examination of scrapings made from the caseous material on the undersurface of the nail plates revealed numerous yeast-like organisms and bacteria. On culture only C. albicans developed.

A third case is that of N. V., a white widow, 51 yr. of age, a hand sewer in a garment factory, who complained about her finger nails. For two months her nails had shown changes, becoming dull, opaque and slightly thickened. The thumb nail on the left hand was extremely thickened, hyperkeratotic, irregular, striated, and dark green. Cultures and smears of the nails, with the exception of the thumb nail, showed no fungi. Smears of the thumb nail showed yeast-like organisms and bacilli. On culture C. albicans and Ps. aeruginosa (Fig. 5) developed.

It is probably safe to assume that, since Ps. aeruginosa is so prevalent in nature, being found in the soil and in the water, and since it may be found on the skin and in the urinary and gastrointestinal tracts, it could easily become a secondary invader in numerous skin lesions. In the cases presented here we feel reasonably sure that the primary nail lesion was caused by the Candida and that Ps. aeruginosa was a secondary invader with the resultant additional nail change, namely, the bluish-green to green color.

SUMMARY

Green nails may be caused by dyes, chemicals other than dyes, various species of Aspergillus, strains of Candida (Syringospora, Monilia) albicans, and by involvement with Pseudomonas aeruginosa (Bacillus pyocyaneus).

Three cases of green nails are presented, one caused by C. tropicalis and Pseudomonas aeruginosa, one caused by C. albicans and one caused by C. albicans and Ps. aeruginosa.

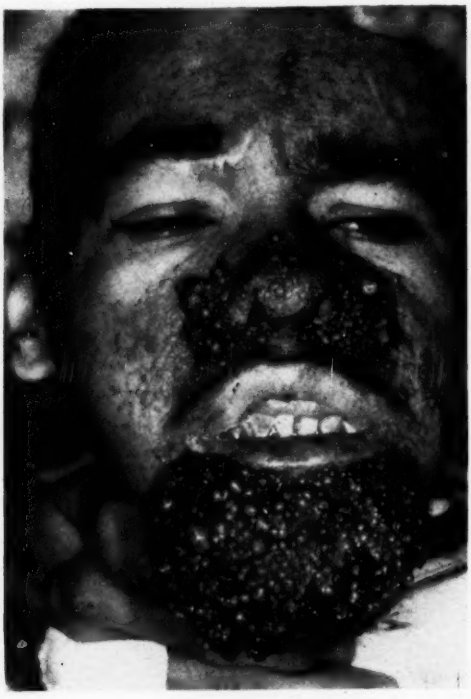
C. tropicalis and Ps. aeruginosa are described.

Clinical Notes

ADENOMA SEBACEUM

ROBERT G. CARNEY, M.D.
IOWA CITY

Adenoma sebaceum is a rather rare developmental anomaly which has been described extensively in the dermatologic literature and, also, because of its association with other developmental lesions, in the psychiatric, neurologic, and other literature. The syndrome epiloia includes adenoma sebaceum and tuberous sclerosis, with mental deficiency and epilepsy.



Adenoma sebaceum.

The typical lesions of adenoma sebaceum appear as small erythematous nodules about the center of the face, and there may be other nevoid lesions, such as pigmented spots, fibromatous nevi, and papillomas. There are frequently tumors and cysts of the heart and kidneys. A case recently studied at the University Hospitals was extreme enough to warrant a case report.

REPORT OF A CASE

D. M., a 20-yr.-old white man, was admitted to the University Hospitals on Aug. 22, 1950, from a state hospital for epileptics and feebleminded, for consideration of treatment of a large grape-like cluster of adenoma sebaceum on the chin (Figure). He was an epileptic with

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a mental age of 4.2 mo., basal age of 2 mo., and ceiling of 7 mo. The patient seemed hardly more than a vegetable, bedridden and helpless, lying curled up, sucking his thumb and drooling. He stared vacantly and did not respond to nonpainful stimuli. No control of urination or defecation was manifested. Physical examination revealed an apical systolic murmur, skin that was sallow and lifeless, and a profound anemia. Covering the entire chin was a mass of small globular tumors, flesh-colored to red, friable and bleeding, and foul-smelling. Smaller similar clusters were present at either side of the nose, and there were discrete papules and nodules on the cheeks and nose. These nodules on the chin and cheeks varied from 2 to 5 mm. in diameter. Lightly pigmented nevoid lesions were noted on the forehead, temples, and occiput, and there was a subungual fibroma on the left fourth finger. Roentgenograms showed multiple small areas of intracranial calcification. The patient was hospitalized for possible removal of the goatee-like mass which had posed a problem in his domiciliary care because of its foul odor and tendency to bleed. On the 10th day in the hospital the patient had a severe and prolonged grand-mal seizure; the following morning he was found dead in bed.

Postmortem examination revealed the cause of death to be an acute right lobar pneumonia. Other significant findings were adenoma sebaceum, tuberous sclerosis, bilateral hamartomata and tubular adenomata of the kidneys, and a patent foramen ovale. No rhabdomyomata of the heart muscle were found. Microscopically, the skin lesions showed mainly fibroblastic proliferation and many thin-walled vessels; there was definite tendency to the formation of keratinized cysts along the ducts of the sebaceous glands, but probably no hypertrophy or increase in number of sebaceous glands, which are large and numerous about the center of the face.

SUMMARY

A case of extremely extensive adenoma sebaceum is presented, with its associated tuberous sclerosis, epilepsy, mental deficiency, and renal anomalies.

University Hospitals.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Maurice J. Costello, M.D., *Chairman*

Wilbert Sachs, M.D., *Secretary*

May 2, 1950

Tuberculosis of Axillary Lymph Node; Phlyctenular Keratitis; Lichen Scrofulosorum; Papulonecrotic Tuberculid; Erythema Induratum. Presented by DR. HARRY L. WECHSLER (by invitation).

L. D., a Puerto-Rican girl aged 15, is presented from New York City Hospital with nonpainful, ulcerated, indurated, erythematous lesions of the calves of the legs, of two months' duration; and a slightly pruritic, grouped, papular eruption of the neck, extremities, and abdomen of one week's duration.

The patient was admitted to New York City Hospital on March 3, 1950. She had enjoyed good health until five years ago, when acute conjunctivitis of the right eye developed that subsided spontaneously. This recurred three and one-half years ago when the patient was hospitalized in another institution for 109 days because of a chronic draining abscess and a mass in the left axilla that failed to heal after surgical incision. Night sweats and anorexia were accompanying symptoms. Guinea-pig inoculation revealed that biopsy material from the draining abscess was positive for tuberculosis. Initial roentgenograms of the chest suggested healing primary tuberculosis, but subsequent plates were read as normal. Treatment in the hospital consisted of administration of ultraviolet irradiation and streptomycin ointment to the axilla. Streptomycin was given parenterally, 100,000 units for seven days, but was discontinued because there was no obvious response. The patient was followed in the outpatient department where the lesions healed after about a year's time.

The present cutaneous eruption started two months ago as a small, discrete, erythematous patch on the posterior aspect of the legs and continued to spread and ulcerate. After a generalized, pruritic, papular eruption developed within one week of the initial visit to the clinic, the patient was admitted to City Hospital for study and treatment.

The patient lived in Puerto Rico until 1946. Her maternal grandfather and uncle had tuberculosis, but the patient had no contact with them. Study of her immediate family in 1947 failed to reveal any evidence of tuberculosis.

Examination on admission showed a well-developed, apparently healthy, 14-yr.-old Puerto-Rican girl. There was a vascularized scarification of the central cornea of the right eye. A firm, walnut-sized node and a well-healed operative scar were present in the left axilla. A generalized, grouped, small, lichenoid eruption was present on the neck and upper extremities. Papules with necrotic centers and inflammatory borders were present on the anterior surface of the legs. A half-moon-shaped, dollar-sized, ulcerated lesion with an erythematous, indurated border was present on the calf of the left leg. An erythematous, indurated, macular lesion on the back of the right leg was beginning to ulcerate. There were a few keloids on the trunk (chickenpox scars).

Reaction of the blood to a Mazzini test was negative, and results of urinalysis were normal. The blood count showed 6,150 white cells with the following percentage distribution: polymorphonuclear leucocytes 46, lymphocytes 48, eosinophils 1, and monocytes 5. The erythrocyte

sedimentation rate was normal. Urine cultures were negative for acid-fast bacilli, as were preparations of material from leg lesions. Roentgenograms of the chest, barium enema, retrograde pyelograms, and gastrointestinal series all failed to show any evidence of tuberculosis. The result of the tuberculin test (1:100,000) was 3+.

A biopsy of sections of skin from the back of the leg disclosed hyperkeratotic epidermis which had undergone acanthosis and parakeratosis. A small papilloma was present, with a cystic comedone-like structure within the cutis. The outstanding changes, however, were deep in the specimen. These consisted of necrotizing panniculitis surrounded by tuberculous granulomatous infiltration. The cutis had in large part been replaced by a vascular scar. The lack of true tuberculous granulation tissue favored a diagnosis of erythema induratum.

Biopsy of other sections of skin disclosed a localized area of epidermal necrosis which penetrated into the cutis and was partly surrounded by edematous, stratified, squamous epithelial cells. Beneath the necrosis there was an infiltration of numerous mononuclear leucocytes, lymphoid and plasmocytic, with a scattering of polymorphonuclear leucocytes. The diagnosis was papulonecrotic tuberculid.

Biopsy of papular lesions of the abdomen was not confirmatory of a diagnosis of lichen scrofulosorum.

Shortly after admission the fine papular lesions became more numerous, and several of the lesions on the extensor surface of the extremities became pustular with a necrotic center. This was associated with a new eruption, similar in appearance, on the back of the legs.

Treatment has consisted of oral administration of concentrates of vitamins A and D daily; crude liver injections twice weekly; and generalized ultraviolet irradiation daily. Tyrothricin compresses applied to the lesion of the left leg helped to clear the secondary infection.

All of the papulonecrotic tuberculids have healed. Those on the anterior tibial areas have left atrophic scars with pigmentation. The lesions on the back of the legs have granulated in and epithelized. The lichenoid lesions have continued to recede in size, leaving only small, slightly elevated papules on the abdomen and about the neck.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: It is interesting to note that she evidently does not have any systemic tuberculosis associated with all these tuberculous manifestations.

DR. CHARLES WOLF: These are hypertrophic scars, and generally in tuberculosis we have depressed scars. The first impression is that we are dealing with one of the anetodermas or atrophodermas. The case demonstrates an unusual manifestation of scars in tuberculosis of the cutis.

DR. FRANK C. COMBES: I agree with all of the diagnoses as presented, with the exception of lichen scrofulosorum. I have seen very few patients with lichen scrofulosorum, and all have been Negroes. This does not represent that eruption clinically, and the diagnosis does not confirm it. I should like to have another biopsy.

DR. HARRY L. WECHSLER (by invitation): The keloidal and hypertrophic lesions are healed chickenpox lesions. The patient does give a history of systemic tuberculosis. Primary tuberculosis was suspected in another hospital and shortly thereafter enlarged axillary nodes were proved to be tuberculous by guinea-pig inoculation. It is interesting to note that the patient shows a hyperallergic reaction to intradermal skin tests with old tuberculin. We will do further histologic studies of the papular lesions.

Dermatitis Herpetiformis with Remission Following Nephrectomy. Presented by DR. DALE D. DOHERTY (by invitation).

N. N., a man aged 65, was admitted to Bellevue Hospital on March 16 complaining of blood in the urine, of eight days' duration. Four months before, the patient had received sulfapyridine for an itchy, generalized eruption of two years' duration. Considerable benefit was obtained from the medication, but it was discontinued because of the appearance of blood in the urine. Urological study revealed a large tumor mass of the left kidney, outlined both on intravenous and retrograde pyelography. The patient underwent a left nephrectomy on April 4, at which time

a large pedunculated tumor mass of the entire lower pole and midpelvis was found. There was no evidence of metastases.

The pathologic report was adenocarcinoma, clear-cell type. Urinalysis on admission showed from 20 to 30 red blood cells per high-power field, and a 1 + reaction for albumin, but results have been normal since the operation.

The patient has received no systemic therapy for his eruption since his admission to the hospital. This was withheld to determine whether or not the surgery would benefit the eruption. At present, one month postoperatively, the patient shows no active lesions of dermatitis herpetiformis.

DISCUSSION

DR. SAMUEL M. PECK: Many of us differentiate our cases of dermatitis herpetiformis (Duhring's disease) roughly into several groups: (1) Typical dermatitis herpetiformis, which is, perhaps, iodide sensitive, comprises the first group. Better than 50 or 60% of patients respond to sulfapyridine or potassium arsenite (Fowler's) solution, plus a maintenance dose. These patients probably manifest a form of bacterid, on the basis of response to a drug such as sulfapyridine. Then, (2) there is a group which, clinically, does not resemble the first. Patients in this group usually have a basal metabolic rate below —20%, a positive finding for potassium iodide test, and a great sensitivity to ordinary skin bacteria. They do well with administration of sulfapyridine, and, so, equally well with small doses of proper bacterial vaccine and thyroid. Then, (3) there is nummular eczema which is also a form of Duhring's disease and is actually a bacterid. Here we have, I think, a proved case in which you remove a focus and the eruption disappears. The late Dr. Hyman also reported such a case.

DR. A. BENSON CANNON†: Will Dr. Peck tell us the clinical appearance of the second group?

DR. SAMUEL M. PECK: The group with the low basal metabolic rate may have classic lesions of dermatitis herpetiformis but with a less marked vesicular element. However, if these cases are followed long enough, vesicles will develop at the point of trauma.

DR. ANTHONY C. CIPOLLARO: When Dr. Peck started classifying dermatitis-herpetiformis-like eruptions I though he was going to go into the group that I have been interested in for almost 15 yr. There are many patients who have lesions which clinically look like dermatitis herpetiformis, and we make such a diagnosis when we see them. These persons should be examined for abdominal tumors. My first experience was with a 13-yr.-old girl with a primary carcinoma of the liver, a diagnosis which was made at autopsy after she died of a ruptured appendix. During life she had an eruption which simulated dermatitis herpetiformis and that diagnosis was made. At present I am following a woman who had a carcinoma of the fundus of the uterus. When the carcinoma was removed, all lesions of dermatitis herpetiformis disappeared. Metastases with ascites developed, and she had a recurrence of the eruption. In the case presented tonight removal of an adenocarcinoma of the kidney caused the disappearance of the dermatitis-herpetiformis-like lesions. I have seen other cases with abdominal tumors, cases with lymphosarcoma with dermatitis-herpetiformis-like lesions. I think we must bear that possibility in mind whenever we see patients who have dermatitis herpetiformis. Then, herpes gestationis probably belongs to the same group. Whatever the modus operandi is, I have not been able to explain it. Abdominal tumors of various types, not necessarily cancers, are associated with severe cases of dermatitis herpetiformis.

DR. MABEL G. SILVERBERG: It is not quite fair to cite one case, but I do know of an instance in which Dr. Sachs thought the eruption was due to cancer at least six years ago, and the patient is still well as far as general health is concerned.

DR. HELEN O. CURTH: I have been interested in dermatoses associated with cancer because of the similarity with acanthosis nigricans. I believe, however, that the dermatosis presented tonight is based on a different principle from that of acanthosis nigricans. I would suggest that the cancerous tumors which have been observed in association with the dermatosis described tonight be listed. In this way, perhaps, one could find the principle which causes the cutaneous eruption.

† Dr. Cannon died on Nov. 27, 1950.

DR. DALE D. DOHERTY (by invitation): Since I am convinced that this eruption was related in some way to the neoplasm of the kidney, and since the type of carcinoma which this man was found to have frequently metastasizes early, it is quite probable that more bullae will appear. In that event, I will certainly send Dr. Sachs a biopsy specimen, if the patient continues under my observation. This patient received sulfapyridine at the Skin and Cancer Hospital for the control of his skin disease. The pruritus was apparently ameliorated by the drug; however, hematuria developed, and an examination of the centrifuged urine specimen, with the Papanicolaou staining technic, showed cancer cells. A review of the American literature of the past 20 yr. showed very few reports of cases similar to this one. There were two cases of chorioepithelioma, three or four of lymphatic leukemia, and only one of carcinoma in association with dermatitis herpetiformis. Reporting of these cases is apparently not as frequent as would be expected from the number of cases cited here tonight. This patient's eruption was certainly typical of dermatitis herpetiformis. Every member of the Bellevue Hospital dermatology service concurred in this diagnosis. There were the usual scratch marks, crusts, pigmentation, and grouping of vesicles over the shoulder blades and elbows.

Exfoliative Psoriasis with Arthritis. Presented by DR. GORDON C. SAUER (by invitation).

L. S., a woman aged 23, is presented from the University Hospital, Skin and Cancer Unit. Her father and grandfather both had psoriasis. At the age of 11 yr. (1938) an eruption developed on her forehead, which soon disappeared. A diagnosis of psoriasis was made by the physician who had treated her father. At the age of 16 she had a similar eruption which did not disappear. She had a severe exacerbation in November, 1946, but improved considerably in the summer of 1947. There was gradual onset of arthritis in November, 1946. In September, 1947, she was married, and about five days later the eruption became generalized. In October, 1947, she had about five months' treatment at Massachusetts General Hospital with baths, hot packs, bed rest, salicylates, vitamins, and blood transfusions. Only wool fat (lanolin) was used locally. After this she went to Florida for 11 mo., and the arthritis developed into the deformans type. Occasionally during the course of the disease her temperature reached 104 F., and she had difficulty in breathing, but no cause could be established for either the fever or the dyspnea. She was hospitalized at University Hospital March 15, 1949. There was a generalized, dry, exfoliative dermatitis with pronounced alopecia. The joints were much as they are today.

The erythrocyte sedimentation rate fluctuated between 36 and 25 mm. per hour during nonspecific therapy and dropped to 1 mm. per hour during corticotrophin (ACTH) therapy. Blood counts and results of urinalysis were essentially normal throughout her hospital stay. The 17-ketosteroids secretion was 3.4 mg. in 24 hr. on admission, and 32 mg. in 24 hr. while on corticotrophin. (Normal for females is 5 to 14 mg.) The sodium-ion concentration in the serum and the chlorides in the urine were normal on admission, but the potassium-ion concentration in the serum was moderately elevated. The total cholesterol and esters were low on admission. The basal metabolic rate was +30%.

Eosinophil counts were studied after administration of many of the drugs in order to determine whether they produced stimulation of the adrenal cortex. Of all the treatments, only epinephrine, autohemotherapy, and corticotrophin caused a consistent fall in eosinophils.

The patient has received adequate courses with what are considered full therapeutic doses of crude liver, desoxycorticosterone acetate in peanut oil with and without vitamin C, para-aminobenzoic acid and sodium salicylate in enteric-coated tablets (pabalate®), pregnenolone (a synthetic steroid compound) with and without vitamin C, vitamin C alone, streptomycin, potassium iodide, lactophenin, sorethytan (20) monooleate ("monitan"), testosterone propionate (oreton®), epinephrine hydrochloride, aureomycin, and lipoadrenal cortex extract, all without favorable response.

Corticotrophin therapy was begun on Feb. 15, 1950, in divided doses every six hours: The first day, 100 mg. was given; the next four days, 62.5 mg. a day; then three days of 25 mg. a day; two days of 12.5 mg. a day, and finally seven days of 50 mg. per day, to a total of 775 mg. over a period of 17 days. The condition of the skin and joints remained static until corticotrophin was begun. Within 24 hr. pain in the joints decreased, and within 48 hr. the skin became much less erythematous, and scaling was less evident. When the dosage was

decreased to 25 mg. a day the skin became more erythematous and papulopustular lesions developed mainly on the flexural areas. The skin again improved when the dosage was increased to 50 mg. a day. All erythema and scaling disappeared, leaving only a dusky hue. The patient was euphoric, and her general outlook was much improved. She was able to crochet and to walk about with comfort for the first time since admission. Within 24 hr. after corticotrophin was discontinued, papulopustules again appeared on the flexural surfaces of the forearms, neck, and chest, and soon the eruption spread over the entire body. Pain in the joints returned shortly thereafter.

In order to prevent immediate recurrence of the dermatitis, administration of lipoadrenal cortex extract was started the same day corticotropin was discontinued, in massive doses said to be comparable to 25 mg. of compound E, and later to 50 mg. of compound E. However, the condition of the skin continued to regress.

While the patient was receiving pregnenolone alone and later with vitamin C, intramuscular abscesses developed, necessitating incision and drainage.

Hydroxyphenyl-cinchoninic-acid therapy was begun on April 13, 1950, with a dosage of 1 gm. daily (20 mg. per kilogram) given within a two-hour period. The dosage was increased to 2 gm. daily on April 18 and continued through April 21, but because of nausea and vomiting it was reduced to 1 gm. daily, which she has received up to the present. On this therapy the skin has become less erythematous, but exfoliation has persisted. Results of liver function tests and urinalyses have remained normal, but the erythrocyte sedimentation rate has increased to 91 mm. an hour.

DISCUSSION

DR. JESSE A. TOLMACH: It should be stated that the response to corticotrophin was most remarkable; within four or five days the entire eruption was almost gone, and after two days the pain was so much relieved that the patient was able to walk about the ward. Within 24 to 48 hr. after the drug was stopped there was a dramatic reversal. In another patient treated with cortisone in full dosage, response did not take place until after 15 days of therapy, with about 75% improvement.

DR. FREDERICK REISS: The improvement in the patients treated with corticotrophin is indeed remarkable. We should discuss the biochemical or immunologic basis of this treatment. Apparently, corticotrophin does not reduce the blood lipids, a factor frequently mentioned as essential for the improvement or cure of psoriasis. One of the most significant phenomena of the effect of corticotrophin is the drop in lymphocytes, which probably acts as an immunizing factor, similar to the action of the gamma globulins. Whether only the lysed lymphocytes should explain the improvement, or whether other cognate immunologic or biochemical changes take place, is still unknown.

DR. FRANCES PASCHER: Desoxycorticosterone acetate and vitamin C, recently advocated for rheumatoid arthritis, have not been effective in this case. Have other members of this Section noted benefit from this combined treatment in psoriasis or psoriasis arthropathica? Dr. Sauer, in recent investigations at the University Hospital, has shown that autohemotherapy is followed by a drop in the eosinophil count similar to that produced by epinephrine and corticotrophin, although to a less extent and less consistently. We know that autohemotherapy has advocates and adversaries; some dermatologists do not use it, others use it as a placebo, and still others consider it of definite therapeutic value. The fact that autohemotherapy is followed by a drop in the eosinophil count appears to support those who maintain that it is of value.

DR. DAVID BLOOM: I saw this patient walking around about 10 days after treatment was started. She looked perfectly normal to me except for the ankylosis of the finger joints. In spite of the fact that corticotrophin has been discontinued, the patient appears much better than before treatment was started. I am much impressed with the possibility that this persistent improvement is due, as the presenter states, to the hydroxyphenyl cinchoninic acid (HPC).

DR. HERBERT SPOOR (by invitation): It was brought out a minute ago that there was a difference between corticotrophin and cortisone, and at the same time it was mentioned that the difference has nothing to do with fat metabolism. There are several other hormones in the adrenal, one of which acts to mobilize fat. The pure hormone has not been isolated as yet.

Maybe the behavior of this particular patient to corticotrophin and cortisone is due to the fact that corticotrophin, in addition to mobilizing cortisone, mobilizes fat factors.

DR. SAMUEL M. PECK: Before we put too much weight on the possible role of the eosinophils and the effect on them of corticotrophin or cortisone, all we have to do is observe the cases of dermatitis herpetiformis that respond to sulfapyridine. The first indication of therapeutic response is an eosinophil drop; if this does not occur, the patient won't respond. I think the eosinophils have no significance whatsoever except as indicating the activity of the disease.

DR. GORDON C. SAUER (by invitation): It has been shown that there is an eosinophilia in dermatitis herpetiformis; so when the disease improves, the eosinophils should fall. Whether it could be stated that the sulfapyridine is acting as a nonspecific stimulant of the adrenal cortex and releasing hormones that cause an eosinopenia I am reasonably sure nobody has determined. With regard to autohemotherapy, Selye has stated that the therapeutic effect of all nonspecific agents might be due to their having stimulated the adrenal cortex. Therefore, I thought it would be interesting to see if autohemotherapy did this. The index used was the fall in number of circulating eosinophils. Twenty subjects were studied, using autohemotherapy and, as controls, epinephrine and saline solution. On the average a 41% fall in eosinophils followed autohemotherapy, a 50% fall followed administration of epinephrine, and an 8% fall followed the saline injection. This would indicate that the autohemotherapy is a mild stimulant of the adrenal cortex. Many other agents can stimulate the adrenal cortex, such as surgery or any stress situation. The eosinophils themselves should be studied much more, especially by dermatologists.

As far as corticotrophin and its effect on lipids is concerned, I was led to believe that the main alteration reported so far has been a fall in the free cholesterol; what the significance is I don't know. Regarding corticotrophin and the proteins, the most consistent changes observed so far have been in acute lupus erythematosus, when there is a fall to normal of the usual high globulin with a correction of the reversed albumin-globulin ratio.

Five patients with psoriasis have also been treated by us with pregnenolone, with or without vitamin C. In three of these patients abscesses developed at the site of injections. Even though we could see improvement in three of the patients (one of whom had an abscess), this took from two to six weeks. Therefore, pregnenolone had probably very limited value.

Parapsoriasis en Plaque. Presented by DR. JOHN DOUGHERTY (by invitation), New York Hospital.
Leukemia Cutis: Aleukemic Lymphatic Leukemia. Presented by DR. ALVO GUIDUCCI (by invitation), New York Medical College Group.
Xanthoma Diabeticorum. Presented by DR. PATRICK BROWN (by invitation), New York Polyclinic Medical School and Hospital.

Paul Gross, M.D., *Chairman*

Anthony C. Cipollaro, M.D., *Secretary*

Nov. 8, 1950

Psoriatic Erythroderma with Arthritis, Treated with Corticotrophin (ACTH). Presented by DR. NATHAN SOBEL.

L. S., a woman aged 23, was previously presented before this section in May, 1950. She had suffered from psoriasis for 12 yr., arthritis for 4 yr., psoriatic erythroderma for 3 yr., and arthritis deformans for 2 yr. There was no response to treatment until corticotrophin (ACTH) was administered. Within 48 hr. after this was begun, the erythema and scaling had greatly lessened, and within a week the skin was clear except for a dusky hue, and the pain in the joints had disappeared entirely. Within 24 hr. after corticotrophin was discontinued, papulopustules developed on the flexural areas, and the eruption became generalized. The joints became painful again after one week. The second course of corticotrophin was begun on July 19, with 25 mg. every six hours (100 mg. a day). She again responded as in the first course. The dosage was then decreased slowly, and the patient was discharged on Aug. 19 with a maintenance dose of 25 mg. intramuscularly twice daily. This dose has been decreased gradually, so that at present she is taking 12.5 mg. twice daily and has been maintained without relapse.

While receiving corticotrophin she has had some hyperpigmentation, especially on the elbows, knees, and back of the wrists. Some hirsutism of the face has developed, which the

patient said she had before she contracted psoriasis, and slight mooning of the face has occurred. She is also taking potassium chloride three times a day, and ascorbic acid, 250 mg. three times a day.

DISCUSSION

DR. J. GARDNER HOPKINS†: It is a very gratifying result. We have one rather stubborn and extensive case of psoriatic erythroderma treated with cortisone, with a result, I must confess, not comparable to this. In other respects our experience differs from the results noted tonight: Rather than being able to reduce the dose, we have had to increase it to get any effect at all, or to maintain the effect. That has been one of the most disturbing problems in our cortisone therapy. We have had to increase the dose until we get a bit terrified. The patient with erythroderma whom we are treating now is getting 500 mg. three times a week and is still not under control.

DR. DAVID BLOOM: A smaller dose of cortisone than the regular amount of 200 mg. a day does not seem sufficient, at least in the case of a young woman with ordinary psoriasis, who had a small number of lesions which had previously cleared up with x-rays and other remedies but which then became resistant to any therapy. During the first week 50 mg. of cortisone was given daily, and during the second week 75 mg. The lesions were not affected in the least. Further treatment had to be discontinued because of a very uncomfortable sensation of bloating in the abdomen.

DR. JESSE A. TOLMACH: I observed a case of psoriasis vulgaris associated with rheumatoid arthritis which was treated with cortisone. The arthritis was relieved but the psoriasis was not only not improved, but became greatly aggravated.

DR. MARION B. SULZBERGER: The response of various dermatoses to these hormones is erratic, and the response to given doses is often an individual matter. Dr. Hopkins said that some of his patients require progressively larger doses, and others seem to be able to reduce their maintenance dose. We have been fortunate in having the latter as a more frequent experience. It is apparent that a vast field of study in dermatology has been opened up here. Even if these materials had done nothing more than to relieve a case of this kind, that would be a tremendous advance. Only those who have seen this young woman languishing in the hospital for years, completely disabled, her painful, red, and desquamating skin distressing her so much that the ankylosed joints appeared not to trouble her at all by comparison—only those can fully realize what this new drug has done for her. I agree emphatically with Dr. Costello; it seems to be the exfoliating erythrodermic psoriasis which responds best to corticotrophin and/or cortisone, whereas the chronic fixed plaques of psoriasis as a rule yield poorly, if at all.

DR. CHARLES WOLF: I believe cortisone and corticotrophin act differently as far as psoriasis is concerned. In corticotrophin there is a lipotropic hormone factor, whereas in cortisone there is none. I believe it will be found that corticotrophin will be the more beneficial. The improvement with corticotrophin varies from slight to marked, whereas with cortisone the patient may be made worse.

DR. J. GARDNER HOPKINS: Will Dr. Wolf enlighten us as to what the lipotropic hormone is?

DR. CHARLES WOLF: The lipotropic hormone is one of the factors or components in the anterior pituitary hormone. It is the secretion which influences fat metabolism, acting on the liver cells.

DR. DANIEL E. HACKBARTH (by invitation): We also treated two patients with the nonarthropathic, plaque type of psoriasis, one with corticotrophin and one with cortisone, and both failed to respond to therapy.

Skin Transplantation in Extensive Vitiligo. Presented by DR. GERALD A. SPENCER.

L. S., a Negro woman aged 43, is presented from the New York Skin and Cancer Hospital complaining of loss of pigment of 15 years' duration. The lesions first appeared on the hands, then extended to involve both limbs, face, and trunk. There is extensive vitiligo on the face, chiefly around the ears, and on the scalp, with poliosis. There are several discrete areas from

†Dr. Hopkins died on Feb. 27, 1951.

pinhead to 50-cent-piece-sized. The arms and chest are dotted with similar depigmented areas. The whole of each forearm has lost its pigment. Most of the cutaneous surface of the lower limbs is involved, leaving almost no unaffected areas.

On June 1, 1950, transplantations of full-thickness grafts were performed. Skin from the scapular area was transposed to a vitiliginous area on the external aspect of the right thigh, and the pathologic skin from this site, also full thickness, was grafted onto the site from which the normal skin was removed. The grafts took successfully, but showed keloid formation which was more pronounced in the scapular area. Both grafts received 1.5 skin units of unfiltered radiation. On Nov. 6 the pathologic graft was still depigmented except for a slight degree of repigmentation at the periphery. The normal skin graft still retained its pigment.

DR. MARION B. SULZBERGER: Experiments of this kind in vitiligo and other dermatoses are rewarding and instructive. Dr. Spencer and the surgeon are to be congratulated on the almost complete "takes" of these transplants, which one doesn't always get. Transplants of this kind have been carried out in various dermatoses, for example, in fixed drug eruptions due to antipyrine or phenolphthalein. The results have not been consistent. In some cases the previously affected skin when removed to a previously normal site became normal, i. e., nonsensitive in its response to a drug; whereas previously normal skin engrafted onto a previously affected site responded to the drug with a reaction of hypersensitivity. In other words, there were results which would suggest that the conditioning of the skin came from below, so that at any given site the transplanted skin reacted in the way the skin previously occupying that particular area had reacted. In other experiments the reverse was found, normal skin grafts remaining normal and hypersensitive skin remaining hypersensitive, no matter where transplanted. I cannot explain the discrepancies except by speculating that conditions of the graft and its "take" might be different from case to case. The cause of, or susceptibility of, the skin to vitiligo in this instance is transplantable, i. e., is inherent in and carried by that thickness of skin which was transplanted. That, I believe, is the important inference from Dr. Spencer's findings, that vitiliginous skin remains without pigment even after months of occupation of a previously pigmented normal site and that, conversely, pigmented skin transplanted to, and healed on, a previous site of vitiligo still maintains its capacity to form pigment unimpaired.

DR. JESSE A. TOLMACH: Previous grafting experiments have been performed in cases of vitiligo. Haxthausen (*Acta dermat.-venereol.* **27**:352-368, 1947) used Thiersch grafts, and Comel (*Dermatologica* **96**:366-372, 1948) used pedicle grafts. Both reported that the grafts took on the character of the new terrain. The result in this case differs from the previous results.

Eosinophilic Granuloma of the Skin, Erythema-Elevatum-Diutinum Type. Presented by DR. JACK WOLF.

F. B., a woman aged 45, is presented from the New York Skin and Cancer Hospital with an eruption of about five months' duration. This consists of two lesions, one on the forehead and the other on the left cheek. The patient attributes these to trauma: In each instance she had attempted to remove a blackhead prior to the development of the lesion. Mild pruritus is the only subjective symptom.

There are two similar lesions, one at about the middle of the forehead, the other on the upper and anterior aspect of the left cheek. The lesions are roughly rounded, approximately 1.5 cm. in diameter, firm and fleshy. The surface is smooth and shiny, and the color, a deep brown with a tinge of red. Fine telangiectases are seen throughout.

Histologic examination revealed a picture consistent with the diagnosis of eosinophilic granuloma of the erythema-elevatum-diutinum variety, as described by Cobane, Straith, and Pinkus (Facial Granulomas with Eosinophilia, ARCH. DERMAT. & SYPH. **61**:44 [March] 1950) and Lever and Leeper (Eosinophilic Granuloma of the Skin, ARCH. DERMAT. & SYPH. **62**:85 [July] 1950).

DISCUSSION

DR. J. GARDNER HOPKINS: There was a group of chronic granulomas of the face presented under a variety of diagnoses because of the different histologic pictures. It is possible that

chronic granulomas of the face take on peculiar characteristics, perhaps because there are so many seborrheic glands in this location. It is necessary to classify these lesions as carefully as we can histologically, but often that does not help us too much in explaining their cause. Are these cases with a few localized lesions related to other cases described as eosinophilic granuloma? I doubt it. The important thing for us to know is, is this a granulomatous process which is entirely benign, or is it an evidence of some systemic hematologic disease?

DR. ARTHUR B. HYMAN: I think the first diagnosis that might be considered is lupus erythematosus. There are cases of that disease with classic lesions which may be associated with infiltrated plaques that present no surface changes. It is also quite possible that one could have such plaques without evidences or ordinary recognizable lupus erythematosus to help us in the diagnosis. Secondly, one might consider benign lymphomas or Spiegler-Fendt sarcoid. Then, there is the question of the relationship of these plaques to eosinophilic granuloma, which in itself is still not a clearly defined clinical entity. The only criterion is the finding of eosinophils in the slide, and if you keep on performing biopsies, a condition which is by definition an eosinophilic granuloma at one time would not be so at another. Moreover, the relationship of the condition to the abstruse erythema elevatum diutinum should be borne in mind. Bismuth will produce good results in some cases. Prolonged observation is needed before the exact place these lesions have in dermatology is established.

Sporotrichosis. Presented by DR. MAURICE J. COSTELLO and (by invitation) DR. JOSEPH I. SINGER.
Benign Acanthosis Nigricans: Mental Deficiency. Presented by DR. HELEN O. CURTH.
Pemphigus Erythematosus Treated with Orally Administered Cortisone. Presented by DR. NATHAN SOBEL.
Vitiligo Improved with Pure Phenol Applications. Presented by DR. GERALD A. SPENCER.
Ring of Comedones Surrounding Irradiated Site. Presented by DR. NATHAN SOBEL.

MANHATTAN DERMATOLOGICAL SOCIETY

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Oct. 10, 1950

Nevoxanthoendothelioma. Presented by DR. DAVID BLOOM.

R. D., a Negro boy aged 2 yr., was seen at the Sydenham Hospital Skin Clinic for the first time in July, 1950, with cutaneous tumors of six months' duration. We were consulted mainly because of a walnut-sized tumor on the vertex which was broadly attached to the scalp, erythematous, and oozing. The other tumors were pea-to-hazel-nut-sized, few in number, and scattered over the scalp and extremities. They were fairly firm and somewhat yellowish and were attached to the skin but not to the underlying tissue.

After biopsy of specimens of the large lesion on the scalp and a lesion on the left knee, the latter area became keloidal, and the lesion on the scalp diminished markedly in size and consistency. In the past few months a few new lesions have developed, one on the anterior lateral aspect of the left thigh which appeared similar to the other lesions, and one on the right forearm which was distinctly subcutaneous but attached to the skin. In addition, there is a lesion anterior to the left ear and one on the right side of the anus.

Because of severe bleeding of the lesion on the scalp during removal of tissue for biopsy, complete blood studies were performed. Bleeding and clotting times were normal, and blood count was normal except for a relative lymphocytosis of 55%. Roentgenograms of the skull and chest were normal.

Histologic examination showed the epidermis to be essentially normal. The cutis showed a large accumulation of mononuclear cells with relatively large, irregularly shaped vesicular nuclei and indefinite cytoplasm outline. There was moderate variability in size, shape, and staining characteristics of the nuclei of these cells. Mitotic figures were frequent. Some multinucleated giant cells were seen, the nuclei of which resembled those of the other cells. In some such giant cells the nuclei assumed a circular arrangement surrounding a central mass of cytoplasm. The cytoplasm was eosinophilic and very slightly granular. A characteristic foam

cell was occasionally seen. The masses of these cells were poorly delimited from the surrounding tissue. Between the masses of cells considerable fibrous connective tisue was present, with densely staining collagen fibers. Sections stained for fat with Sudan IV revealed small quantities of lipid material in fine granular form within the cytoplasm of many cells. Pathologic diagnosis was xanthoma.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: It is certainly unusual to see patients with this disease on two successive weeks. I presented a case from the New York Hospital last week at the New York Academy of Medicine in a white child, in whom the color of the lesions was more typical because it was not masked by the color of the skin. The lesion on the scalp, I thought, was unusual. It would be difficult to make a diagnosis of that disease on the scalp lesions if it were not for the biopsy. As to the management of the case, so many persons with this condition get well spontaneously that no special treatment is required.

DR. DAVID BLOOM: The large, raised, oozing, and bleeding tumor on the vertex made the surgeons suspect cancer before consultation from the dermatology clinic was requested. The other lesion on the skull and those on the body reveal the diagnosis of nevoxanthoendothelioma. Even textbooks confuse this disorder with xanthoma tuberosum. In the latter, the lesions are mostly present over areas of pressure, such as over tendons and the lower part of the buttocks; they are associated with hypercholesteremia and are hereditary. In contrast to xanthoma tuberosum, the lesions in nevoxanthoendothelioma have a tendency to disappear.

Schamberg's Disease (Progressive Pigmentary Dermatosis). Presented by DR. MAURICE J. COSTELLO.

G. V., a woman aged 54, had had a generalized, somewhat pruritic eruption for five months when first seen on Jan. 14, 1949. The eruption at present consists of a number of irregular erythematous purpuric lesions on the thighs and legs.

Biopsy, performed June 22, 1950, revealed an epidermis which could be regarded as normal for a thin-skinned part of the body. The main pathologic process concerned the blood vessels. In the subpapillary region and extending only somewhat into the papillae, the capillaries were strikingly hyperplastic. They followed a tortuous course, and they had slightly thickened but rigid-appearing walls and small but altogether-patulous lumens. There was only a scanty inflammatory-cell infiltration around them and only a suggestion of edema. That is, it was a matter of vascular abnormality, pure and simple, with only a modicum of inflammatory reaction. Indeed, fibroblasts were more conspicuous at some places than were the infiltrative cells. There were no hemorrhages or blood pigmentation. The pathologic diagnosis was "capillary hyperplasia and fibrosis, Schamberg's disease probable." The absence of an adequate inflammatory infiltrate would exclude poikiloderma atrophicans vasculare.

Treatment has consisted of generalized ultraviolet irradiation, liver extract and estradiol benzoate (progynon-B®) given intramuscularly, nicotinamide given intravenously, and diphenhydramine (benadryl®) hydrochloride and hesperidin by mouth.

DISCUSSION

DR. SAMUEL M. PECK: The whole group of capillary diseases has been separated into definite entities which are based on clinical and pathologic findings. Capillary tests also help to differentiate some of these diseases. In my opinion, Schamberg described a definite disease entity which is familial, begins on the lower portion of the leg, and is characterized by capillary hemorrhages. The vascular changes are less pronounced than in Majocchi's disease. There are no degenerative changes of the endothelial cells lining the capillaries. Long-continued administration of moccasin venom will bring about remissions. If you examine any part of this patient's lesions, it could fit in with Schamberg's disease.

DR. WILBERT SACHS: I cannot add anything to what Dr. Wise wrote about this group of diseases. I had something to do with the pathologic studies in those cases.

DR. PAUL E. BECHET: The patient presents many dilated venules and pigmentation. The pinpoint- to pinhead-sized reddish puncta and areas of pigmentation are also present in the symptomatic purpuras and in the areas of dilated venules and capillaries on the lower third of

both legs in people who stand a great deal, particularly obese elderly housewives. It seems to me, because of the striking resemblance to one another of the simple local purpuras, telangiectatic areas, hemostatic eczema and dermatitis, and Schamberg's disease, that this whole group of hemostatic phenomena could be classified under the simple head of dermatitis hemostatica, as suggested by Wise. I would not include purpura annularis telangiectodes in this group, as that dermatosis is a definite clinical entity, presenting a characteristic symptomatology which differs entirely from the other disorders mentioned.

DR. WILBERT SACHS: Schamberg's disease and the purpuras involve the capillaries, and the others the small arterioles. In Schamberg's disease there is a superficial inflammatory process.

DR. FRANK C. COMBES: The differential diagnosis lies between orthostatic purpura and Schamberg's disease. In this respect I should like to ask Dr. Peck, who has had a lot of experience, whether moccasin venom would be of any aid in differentiation. In my experience both diseases give positive tests on the lower extremities and negative on the upper extremities.

DR. SAMUEL M. PECK: Schamberg's disease is still very much a question of clinical diagnosis in spite of biopsy findings. Capillary fragility, when demonstrable, is present in the vicinity of the lesions only. The disorder is usually progressive, and I have seen it improve under snake-venom therapy only after months of treatment.

Spiegler-Fendt Sarcoid. Presented by DR. NATHAN SOBEL.

R. H., a woman aged 53, was first seen Aug. 28, 1950, at the Skin and Cancer Unit, New York University-Bellevue Medical Center, with an eruption of one year's duration. The patient has lesions on the left cheek in two areas; one lesion is the size of a nickel and located below the malar prominence, and the other, the size of a dime, is 1 in. (2.5 cm.) in front of the left ear lobule. Each area is composed of small papules, pinpoint-sized to large pea-sized, though most are 1 mm. in diameter. Some lesions are individual, others are confluent. The lesions are elevated, infiltrated, and brownish, and on diascopic pressure a brownish-red infiltrate is seen. A few scattered lesions are present on the right cheek. In the region of the left sternoclavicular joint a similar dime-sized patch is present.

There were 4,300,000 red cells, hemoglobin 11 gm., or 76%, and white cells, 7,500, with polymorphonuclear leucocytes 59%, lymphocytes 34%, monocytes 5%, basophils 1%, and eosinophils 1%. Results of intradermal tuberculin tests made on Sept. 15 were negative in dilutions of 1:1,000,000 and 1:100,000, and positive at 1:10,000.

Biopsy findings on a specimen from a lesion over the sternum were reported by Dr. Charles Miller to show, throughout the corium and down to the fat, well-defined cell masses, consisting mostly of lymphocytes. In some of these masses two cell types could be seen, one having larger, pale-staining nuclei making up the center, which was surrounded by the other type of cells, mainly lymphocytes. Some mitoses could be seen. Besides those well-defined cell masses, similar, less-well-defined areas of lymphocytes could be seen around dilated blood vessels. The overlying epidermis was thinned and showed pronounced pigmentation of the basal cell layer. Histologic diagnosis was Spiegler-Fendt sarcoid.

DISCUSSION

DR. WILBERT SACHS: The microscopic picture is typical of Spiegler-Fendt sarcoid.

DR. GEORGE M. LEWIS: The satellite or small discrete lesions present on the left cheek resemble those in a patient I observed and reported some years ago, in whom the lesions were present in the inframammary region. The biopsy specimen which Dr. Sachs saw then, also showed a histologic structure similar to the one under the microscope tonight. It is my impression that the disease process in this patient runs a comparatively benign course and should be differentiated from lymphosarcoma, in which the outcome is fatal. I followed one patient for 15 yr., and there was no recurrence. The majority of such patients respond rapidly to small doses of low voltage x-rays, and I would predict a good response to such therapy in this patient.

DR. ANTHONY C. CIPOLLARO: This is a rare disease, and I think it is well to discuss one or two more points. Spiegler-Fendt sarcoid frequently resembles the localized form of lupus erythematosus or the lichenoid or the Boeck type of sarcoid. I also followed one patient for

about 15 yr., and I think Dr. Lewis included that patient in his report. This patient had lesions on the face, just as the woman shown tonight, and they would disappear with administration of rather small amounts of x-rays. She had recurrent attacks, and the lesions would not appear at the same sites, but always on the face or chest. Each time they appeared, a specimen of one was removed for biopsy, and the others were treated with x-rays. Biopsy always showed Spiegler-Fendt sarcoid. My patient never had the severe generalized lymphoblastoma that one fears in this type of disease.

DR. PAUL GROSS: The satellite lesions to which Dr. Lewis referred seem quite characteristic of this disease. The clinical resemblance to Boeck's sarcoid, together with the histologic findings suggesting a lymphoblastoma, justify the diagnosis.

DR. NATHAN SOBEL: My understanding is that there is no particular type of reaction to tuberculin test in this condition as there is in Boeck's sarcoid, which usually is characterized by a negative reaction.

Reticulum-Cell Sarcoma. Presented by DR. FRANK C. COMBES.

J. R., a man aged 53, presents several smooth, dusky-red, slightly tender tumors in the right flank, of 15 years' duration. They vary in size but slightly, averaging in diameter the size of a man's fist. Some are confluent.

Cytologic and chemical examination of the blood was normal. Several doses of filtered roentgen irradiation and injections of antimony potassium tartrate were without effect. Therapy with corticotrophin, a total dose of 1,550 mg. over a period of two weeks, caused about 10% regression in size.

DISCUSSION

DR. WILBERT SACHS: Has anybody seen a reticulum-cell sarcoma last 15 yr.?

DR. NATHAN SOBEL: I do not know how long they last, but I have a patient on the wards at University Hospital whose condition was treated for years as mycosis fungoides, definitely established by biopsy. It extended around the eye, and we thought it might involve the eye. He was hospitalized. Then more lesions appeared all over the body, and finally a diagnosis of reticulum-cell sarcoma was established. He has had corticotrophin (ACTH) without any improvement.

DR. WILBERT SACH: The history favors the diagnosis of mycosis fungoides.

DR. ANTHONY C. CIPOLLARO: Clinically, I would put this in the category of mycosis fungoides, and that is what I think this patient has. There are patients with mycosis fungoides d'emblee who do not respond to irradiation, and this one did not.

DR. PAUL E. BECHET: I agree with Dr. Combes' diagnosis. The tumor does not in the least resemble either mycosis fungoides of the d'emblee or Vidal-Brocq type, or the tumor stage of ordinary mycosis fungoides, in which the tumors are highly inflamed, moist, oozy, fungating masses which break down easily. The tumor in Dr. Combes' patient is a livid color, soft in consistency, and without the slightest evidence of acute inflammation.

DR. ISADORE ROSEN: I agree with the remarks made by Dr. Bechet. The location, the clinical features, and the involvement limited to one area for so many years without ulceration would be very unusual for mycosis fungoides. It would probably fit in with one of the other types of lymphoblastoma.

DR. FRANK C. COMBES: I agree with those who feel that this dermatosis does not particularly resemble mycosis fungoides, even the tumor d'emblee type. Rather it resembles some other lymphomatous disease. The diagnosis of reticulum-cell sarcoma was made histologically and not clinically.

A Case for Diagnosis (Lupus Erythematosus? Basal Cell Epithelioma?). Presented by DR. WILBERT SACHS.
Epidermodysplasia Verruciformis. Presented by DR. FRANK C. COMBES.
Epidermolysis Bullosa Hereditaria. Presented by DR. ANTHONY C. CIPOLLARO.
Erythema Annulare Centrifugum. Presented by DR. JACK WOLF.
A Case for Diagnosis (Keratosis Blennorrhagica?). Presented by DR. ORLANDO CANIZARES.
Dermatitis Factitia. Presented by DR. ORLANDO CANIZARES.
Erythema Elevatum Diutinum. Presented by DR. THOMAS N. GRAHAM.
Extensive Keratoses with Epithelioma. Presented by DR. MAURICE J. COSTELLO.

SAN FRANCISCO DERMATOLOGICAL SOCIETY

Stuart C. Way, M.D., *President*

Rees B. Rees, M.D., *Secretary-Treasurer*

Nov. 17, 1950

A Case for Diagnosis (Keratoderma Palmaris? Mal de Meleda?). Presented by DR. ROBERT WALTON (by invitation).

A. I., a 26-yr.-old Japanese woman, first noticed thickening of the skin of her palm when she was 6 yr. old. She does not recall at what age her fingernails become dystrophic. Her palms perspire. A diagnosis of mal de Meleda was made by Dr. Niles and Dr. Clump in 1948. Biopsy findings were consistent with this diagnosis. There is no history that anyone else in the family had this condition.

In addition, this patient has had hundreds of small flat warts covering her face and hands. This condition began seven years ago and has been refractory to numerous forms of therapy, such as x-ray, liquid nitrogen, smallpox vaccination, bismuth, electrolysis, and rat-wart toxin.

DISCUSSION

DR. REES B. REES: This case does not resemble those cases of mal de Meleda I have seen, and the lack of family history also speaks against it. The progenitors of this disease come from a very small geographic area. I do not know whether this woman comes from there or not.

DR. ROBERT ALLINGTON: As far as I know mal de Meleda is not limited exclusively to those whose families originally came from Meleda. His race alone would not prevent a Japanese from having this disease.

DR. FRANCES KEDDIE: I would call it epidermodysplasia verruciformis.

DR. ROBERT WALTON (by invitation): There are only five cases of mal de Meleda reported in American literature, none in the British, but several in the French and German. People who have written on this subject in American literature have made four points of difference between mal de Meleda and the keratoderma of the palms and soles as described by Unna. These points of difference are as follows: In mal de Meleda there is excessive sweating of the palms and soles, producing an odor like rancid butter; an erythematous border surrounds the hyperkeratotic patches; the condition is inherited on a basis of a recessive gene and not a dominant gene, and, finally, there is hyperkeratosis on other parts of the body besides the palms and soles. Mal de Meleda was originally described in the people of the island of Meleda but later was reported by German and French writers in other parts of Europe in different races. In this patient there is no excessive sweating and the lesions are confined to the palms, and, if one is going to differentiate mal de Meleda from keratoderma (Unna), then this woman probably has the latter condition rather than the former.

Localized Myxedema. Presented by DR. JAMES MCGINLEY (by invitation).

A 38-yr.-old white man contracted classic thyrotoxicosis in December, 1946. He was prepared with strong iodine (Lugol's) solution, and a thyroidectomy was performed in August, 1947. Mild exophthalmos appeared preoperatively and became worse two or three months after the operation. At the same time as exacerbation of the exophthalmos, the patient noted nodular swellings on both lower legs which have remained static until the present time.

There are nodular, firm, slightly bluish, nonpitting masses on the anterolateral surface of the left leg, on the lower third and just above the external malleolus. There is marked exophthalmos.

The I^{131} uptake was increased above the upper limits of normal. The microscopic sections were diagnostic of localized myxedema.

The lesions on the left leg were inoculated with 4 cc. of hyaluronidase (500 turbidity clearing units per cubic centimeter) after preliminary injection of procaine hydrochloride on Nov. 7, 1950. An immediate softening of the lesion was noted; there was an inflammatory reaction and edema the next day. Five days after the injection the patient was seen again, and the lesion

was only one-fourth of its original size. The patient was given an injection on Nov. 16, 1950, of 1,600 units of hyaluronidase into the upper left lesion and 2,400 units into the lower left lesion.

DISCUSSION

DR. STUART WAY: Several years ago I presented a similar case in a Chinese boy. The lesions developed after a thyroidectomy and disappeared without therapy. Thyroid extract produced a tachycardia and could not be used.

DR. JAMES MCGINLEY (by invitation): Credit for the slides with the demonstration of the specific effect of hyaluronidase on the mucopolysaccharides of localized myxedema belongs to Dr. Abdul Haj of the pathology department of the University of California. We have also stained orbital tissues from patients with malignant exophthalmos and demonstrated the marked accumulation of mucopolysaccharides which would develop when treated with hyaluronidase. Further work is being carried out in this condition and its pathologic-physiologic relationship to localized myxedema.

Congenital Ichthyosiform Erythroderma. Presented by LIEUTENANT COLONEL ROBERT HIGDON, M.C., U.S.A.
A Case for Diagnosis (Cheilitis Exfoliativa? Cheilitis Glandularis? Erythema Solare? Lupus Erythematosus? Squamous Cell Carcinoma?). Presented by DR. EDWARD RINGROSE and DR. GORDON EKBLAD.
A Case for Diagnosis (Granuloma Annulare?). Presented by DR. ROBERT ALLINGTON.
A Case for Diagnosis (Psoriasis, Pityriasis Rubra Pilaris?). Presented by DR. EDWARD RINGROSE.
Parapsoriasis. Presented by DR. GEORGE KULCHAR.
Lupus Pernio (Schaumann's) (Erythema Induratum?). Presented by DR. ARNE INGELS.
Chronic Discoid Lupus Erythematosus with Dissemination. Presented by DR. EUGENE FARBER.
Tuberculosis Verrucosa Cutis. Presented by DR. ARNE INGELS.
Chronic Erythema Multiforme. Presented by DR. BERNARD RYAN.

Stuart C. Way, M.D., *President*

Rees B. Rees, M.D., *Secretary-Treasurer*

Jan. 19, 1951

Kaposi's Multiple Idiopathic Hemorrhagic Sarcoma. Presented by DR. EUGENE FARBER.

DISCUSSION

DR. EUGENE FARBER: This is an interesting case. There are so many discrete lesions, and they are so widely distributed that the use of x-ray does not seem practical. We have used cortisone for two weeks but it has not accomplished anything. Kaposi's sarcoma is hard to understand. It is thought that various areas arise simultaneously and that the disease may remain benign for a long time. If active sarcoma develops, metastases then occur. Various organs, such as liver, spleen, and skin, may be involved, and the metatastic lesions then grow rapidly in multiple sites. Ulcerations are now developing on the toes, and the patient is beginning to have pain.

DR. CHARLES LINCOLN, JR.: Another possible suggestion, if one wishes to reserve x-ray treatment until the patient is having great difficulty, is to use estrogens. I know of two patients treated in this way. The use of estrogens makes sense, since this disease does not occur in women or, in any case, is very rarely seen in women.

DR. JOHN SKAHEN: Considering the rather grim long-term outlook for persons with Kaposi's sarcoma, one might consider using Shearer's polysaccharide later when the disease is incapacitating the patient. This is rugged treatment, but so is the disease. This treatment has caused remissions, though no real reported cures, in reticulum-cell sarcoma and other lymphomas. As you know, Kaposi's sarcoma has been classed as one of the lymphomas by such persons as Ewing.

A Case for Diagnosis (Lymphangiomatous Nevus?). Presented by DR. EDWARD RINGROSE and DR. GORDON EKBLAD.

G. M., a 15-yr.-old white boy, has noticed an abnormality of the lips for as long as he can remember. He has been told to use chap sticks, which he has done for some years with no benefit. This has been the only treatment used. The only symptom is a mild dryness of the lips.

On examination there is marked papillary hypertrophy of the entire lower lip, extending for a short distance onto the buccal mucosa. The upper lip is similarly involved in its posterior

portion. There is slight furrowing of the tongue. The patient is seen to purse his lips rather frequently; this may be a habit or a response to dryness.

The medical history is otherwise noncontributory, except that during the past three months the patient has had four episodes of hematuria. He has not been seen during an attack, and between attacks the urine is normal. Intravenous pyelograms showed no abnormality.

Histological examination of a section of the lower lip revealed marked irregular acanthosis and papillomatosis. There was moderate parakeratosis. There was marked intracellular and intercellular edema throughout the epidermis. There was a marked increase in the number and size of the lymphatics in the upper portion of the cutis. These were associated with a prominent inflammatory infiltrate of lymphocytes, plasma cells, and polymorphonuclear leucocytes. A section stained for fat revealed no abnormality of fat distribution.

DISCUSSION

DR. FRANCES TORREY: I agree with the diagnosis. One might consider the excision of the mucous membrane that is involved, with advancement of the mucous membrane within the mouth because of the defect. This seems to be the best way of removing a lesion of this sort.

DR. EDWARD RINGROSE: I wish to thank Dr. Torrey for this suggestion. Dr. Ekblad suggested the same thing. However, when one examines the patient closely, there appear to be some changes in the mucous membrane inside the mouth which may represent the same disease process, and if the mucous membrane were advanced, he might manifest the same condition all over again. There is probably some hypertrophy of the lesions due to his habit of pursing his lips. This may be just a habit, although, if he goes for three or four hours without pursing his lips or moistening them, they tend to dry and stick together.

DR. GORDON EKBLAD: This lesion does seem to be too deeply situated and extensive to shave it all off and advance the mucous membrane without having it regrow. However, this may be tried.

Mycosis Fungoides. Presented by DR. EDWARD RINGROSE.

F. S., a 72-yr.-old white American fertilizer salesman, for 20 yr. has had scattered skin lesions, a specimen of which was removed for biopsy in October, 1941, and showed changes characteristic of mycosis fungoides. From 1941 to 1949, each lesion as it appeared was treated with radiation with temporary satisfactory results. He has now had a maximum dose of x-rays.

Findings from the physical examination were essentially normal except for the skin, which shows irregular dry papulosquamous areas on the trunk with infiltrated weeping areas on both thighs and ulceration on the medial side of the left thigh.

The laboratory findings have been normal. A recent blood count was as follows: 6,800 leucocytes, 61% neutrophils, 6% eosinophils, 1% basophils, 30% lymphocytes, 1% monocytes, and 13.5% hemoglobin.

Recent treatment has consisted of ultraviolet irradiation, started about one month ago, with improvement.

DISCUSSION

DR. CHARLES LINCOLN, JR.: There is no doubt as to the diagnosis. I am curious as to whether "stibanose" (diethylaminoethanol salt of sodium antimony gluconate) has been used for this disease in this area. Dr. Garbe in New York has used "stibanose," and the possibility of using antimony potassium tartrate, stibophen (fuadin®), or other antimony preparations might be considered. Dr. Garbe obtained some nice results which I was fortunate enough to see. It probably is inferior to treatment with x-rays or radioactive substances, but this point should be determined.

DR. HERMAN ALLINGTON: We used "stibanose" on one patient for several weeks after corresponding with Dr. Garbe on the subject. There was no benefit.

DR. FRANCES KEDDIE: I have had occasion to treat a patient with "stibanose," but after three weeks he became nauseated, and jaundice developed.

DR. M. F. ALLENDE: Dr. Garbe obtained good results in the first three cases but subsequently treated seven more patients without benefit, and in a second paper he corrected some of the statements he originally made.

DR. EDWARD RINGROSE: I appreciate the comments. The possibility of using "stibanose" will not be considered after what has been said. Dr. George Kulchar suggested the use of ultraviolet rays on the basis of their having seemed valuable to some Eastern dermatologists.

DR. CHARLES LINCOLN, JR.: Dr. George Andrews has used ultraviolet rays for many years in this disease. He attempts to control the patient's lesions with ultraviolet rays for as long as possible and then gives x-ray therapy. X-rays are more effective because they will control the disturbance even after the ultraviolet rays fail to do so.

DR. ERVIN EPSTEIN: At the meeting of the Pacific Coast Dermatological Association in October Dr. Paul O'Leary recommended the use of ultraviolet rays for this disease. The patient with mycosis fungoides that I presented at that meeting has been getting ultraviolet rays in the form of sunlight and has been doing excellently.

DR. EUGENE FARBER: The patient to whom Dr. O'Leary refers was at the Mayo Clinic while I was there. When he obtained a good tan the lesions would tend to subside. This man has shown a small amount of improvement on ultraviolet ray therapy. He has already had as much as 9,000 r to two lesions on his right thigh.

DR. MORTIMER FALK: Has cortisone or corticotrophin (ACTH) been used for this disease?

DR. GEORGE WILSON: In the issue of the *Journal of Investigative Dermatology* for November, 1950, a remission has been described in three patients as long as they received cortisone or corticotrophin (Tulipan, L.: *J. Invest. Dermat.* **15**:349, 1950). They were given the drug for a period of four days to two weeks. The drugs definitely seemed to give temporary improvement in these patients but then resulted in failure.

DR. ERVIN EPSTEIN: I asked Dr. O'Leary if I should give my patient cortisone or corticotrophin, and he advised against it.

DR. GORDON EKBLAD: We have tried treating one patient with a case of 25 years' standing with an extensive course of cortisone, with no benefit even while on treatment.

Lupus Vulgaris. Presented by DR. PAUL FASAL.
Unusual Case of Seborrheic Dermatitis (Darier's Disease?). Presented by DR. ARNE INGELS.
A Case for Diagnosis (Erythroderma Congenitale Ichthyosiforme? Ichthyosis?) (Pityriasis Rubra Pilaris?). Presented by DR. JULIAN LUNSFORD.
A Case for Diagnosis (Parapsoriasis?). Presented by DR. ROBERT ALLINGTON.
Mycosis Fungoides. Presented by DR. HERMAN ALLINGTON.
Lupus Erythematosus, Chronic Generalized Type, Improved from Cortisone. Presented by DR. ROBERT WALTON (by invitation).
Familial Hemorrhagic Telangiectasia (Rendu-Osler-Weber's Syndrome). Presented by DR. GILBERT BEIRNE (by invitation).
A Case for Diagnosis (Disseminated Xanthomatosis? Eosinophilic Granuloma?). Presented by DR. OTTO SCHMIDT.

DETROIT DERMATOLOGICAL SOCIETY

Arthur E. Schiller, M.D., *President*

C. J. Courville, M.D., *Secretary*

Roy H. Holmes, M.D., *Recorder*

Jan. 10, 1951

Onycholysis with Pigmentation. Presented by DR. CHARLES J. COURVILLE.

A white woman, aged 25, is presented, with orange and brownish discoloration and varying degrees of separation of the nail plates of all fingernails of both hands, which began six weeks ago and extended to all fingernails. She has been using various unnamed types of nail polish and nail-polish base. There is no history of trauma or other disease except asthma. The toe nails are not affected. No other skin lesions are seen.

DISCUSSION

DR. HERMAN PINKUS: Base coats can impart permanent luminescence to fingernails under filtered ultraviolet light rays. The color effect resembles that caused by ingestion of quinacrine (atabrin®) hydrochloride. The base coats themselves are not luminescent and do not change

the appearance of the nails when freshly applied. Either these plastics cause some change of the nail substance, or they permit a fluorescent dye which may be in the nail enamel to become fixed in the nail.

Universal Exfoliative Psoriasis Successfully Treated with Cortisone. Presented by DR. A. E. SCHILLER and DR. H. H. HOLMAN.
Keratosis Follicularis. Presented by DR. C. J. COURVILLE.
Psoriasis Benefited by Doses of Vitamin A. Presented by DR. C. K. HASLEY and (by invitation) DR. A. E. GULICK.
Pustular Bacterid? Pustular Psoriasis? Presented by DR. A. E. SCHILLER and DR. H. H. HOLMAN.
Amyloidosis Cutis? Chronic Neurodermatitis? Presented by DR. C. J. COURVILLE.
Trichoepithelioma(?). Presented by DR. ALICE E. PALMER.
Scleroderma(?). Presented by DR. G. B. SEXTON, London, Ont., Canada.
Pemphigus Vulgaris Responding to Cortisone. Presented by DR. LOREN SHAFFER.
Contact Dermatitis? Dyshidrosis? Presented by DR. C. K. HASLEY and (by invitation) DR. A. E. GULICK.
Sarcoidosis (Pulmonary and Cutaneous). Presented by DR. A. E. SCHILLER and DR. H. H. HOLMAN.
Lichen Planus Linearis? Nevus Unius Lateris? Neurodermatitis? Presented by DR. A. E. SCHILLER and DR. H. H. HOLMAN.
Epidermolysis Bullosa, with Partial Genealogical Chart. Presented by DR. C. J. COURVILLE.
Lupus Erythematosus? Parapsoriasis? Presented by DR. CHESTER SIDELL, Grand Rapids, Mich.
Mikulicz' Syndrome(?). Presented by DR. CLYDE HASLY.
Papulonecrotic Tuberculids(?). Presented by DR. ALICE E. PALMER.
Chalazion(?). Presented by DR. HERSHAL S. ZACKHEIM.
Purpura Annularis Telangiectodes (Majocchi) (?). Presented by DR. A. E. SCHILLER and DR. H. H. HOLMAN.
Chronic Familial Benign Pemphigus (Hailey-Hailey Disease). Presented by DR. A. E. SCHILLER and DR. H. H. HOLMAN.
Chronic Familial Benign Pemphigus (Hailey-Hailey Disease). Presented by DR. ALICE E. PALMER.

BROOKLYN DERMATOLOGICAL SOCIETY

I. N. Holtzman, M.D., *President*

C. B. Locasto, M.D., *Secretary*

Jan. 16, 1951

A Case for Diagnosis: Scleroderma Improved with Cortisone. Presented by DR. M. SILVERMAN.

DISCUSSION

DR. S. H. SILVERS: There is no question that this girl has improved both subjectively and objectively. Those of us who have seen her for a long time have noticed both objective and subjective improvement since treatment with cortisone has been instituted. However, the improvement may be due to the mobilization of water in the subcutaneous tissues. That may account for the increase in the softness of the skin and the filling-out effect on the face and the body. The fact is that she can now do many things, such as buttoning her blouse, walking, and sitting up in a chair and bending.

A Case for Diagnosis: Dermatomyositis Improved with Cortisone. Presented by DR. M. SILVERMAN.

On Nov. 17, 1950, five weeks after the patient's admission cortisone therapy was started. The sedimentation rate at this time was 24 mm. in 45 min. After four days of cortisone therapy, the patient improved remarkably and for the first time since admission was ambulatory. The patient was maintained on 100 mg. of cortisone daily, and three weeks later the dosage was cut to 50 mg. daily. Two days after the reduction of cortisone, a generalized erythroderma developed, more extensive than on admission.

At present the patient is being maintained on 100 mg. of cortisone daily. She is clinically much improved, her erythema has faded markedly. The sedimentation rate is 16 mm. in one hour.

DISCUSSION

DR. JOEL SCHWEIG: I have also noticed some patches on the neck consisting of telangiectases, causing a mottled appearance of the area, adding a poikilodermatous feature to the eruption. The diagnosis of poikilodermatomyositis would fit the case much better. This is a serious disease, and all the patients that came under my observation succumbed within several months after the onset of the disease. It is highly gratifying to see such a dramatic improvement from cortisone in a hitherto intractable disease.

Pemphigus Vulgaris. Presented by DR. C. T. CHIARAMONTE.

The patient has been maintained almost continually on aureomycin (one year). When the dose is less than 750 mg. per day, there are new crops of bullae. Doses above 750 mg. seem to keep him free of bullae.

DISCUSSION

DR. C. T. CHIARAMONTE: The patient began to respond immediately when aureomycin therapy was begun, and each time the drug was stopped the bullous lesions reappeared copiously. We are now attempting to establish a maintenance dose of aureomycin. He has gained much weight. I think this is a striking example of the beneficial action of aureomycin in pemphigus vulgaris. He had 500 mg. four times a day in the beginning and then gradually 250 mg. two times a day. He can be maintained on 750 mg.

A Case for Diagnosis: Senear-Usher Syndrome? Presented by DR. M. SILVERMAN.

D. L., a white woman, aged 56, entered the hospital on Jan. 9, 1951, with the chief complaint of itching and vesicle formation of scalp, face, neck, and chest. In August, 1950, she first noted the sudden onset of vesicle formation and pruritus over the right eyebrow. This progressed until it involved the entire right forehead. The patient was treated with various salves, and the lesions soon spread to involve the scalp, face, neck, thorax, and back.

The patient claims to be allergic to raspberries and nylon. She has had recurrent attacks of bronchitis for 20 yr. and intermittent periods of eczema over the arms and legs for the last 18 mo.

On admission the patient was noted to have a large erythematous lesion over the right forehead and face which seemed denuded of epidermis and was slightly weeping and pruritic. There are areas of erythema, exudation, and old bullae, infraorbitally as well as around the nostril. The hair is mottled and the scalp covered with crusts, which on being lifted reveal raw exudative areas. The neck and upper chest and back show many excoriations and evidences of old healed, ruptured bullae.

All laboratory findings have been essentially normal. A biopsy has not yet been done.

DISCUSSION

DR. ABRAHAM WALZER: The French, especially Civatte, have been doing some work in the last 10 yr. on the question of the histopathology of the skin in pemphigus. They showed that the primary lesion of true pemphigus is not a bulla. They showed that the primary lesion is an acantholysis within the prickle-cell layer and that these changes produce the separation of the prickle-cell layer, and then edema, coming from the vessels below, permeates into this break and raises it and gives the intradermal bullae. They say that this is the characteristic formation of bullae of pemphigus. Occasionally one will see bullae in pemphigus in which the base of the bullae is subcutaneous. These are due to the fact that in some of these cases the edema is of considerable amount and the bullae may be extended and stretched, thus giving a subcutaneous bullae. The lining (which is the important part) of the floor and top of this bulla, consists of these degenerative cells, and if these can be demonstrated in histologic sections, the condition is pemphigus. On the other hand, failure to find this condition does not rule out pemphigus. But if it is found, the disease is pemphigus. In erythema multiforme and dermatitis herpetiformis, the lining of the bullae is composed of different inflammatory cells. Later, the French showed that simply by scraping the floor of the bullae, the acantholytic cells also can be demonstrated. The negative findings are not as important as the positive ones. In the *British Journal of Dermatology,* (Rook, A. J., and Whimster: *Brit. J. Dermat.* **62**:443, 1950) Rook and his associate also demonstrated these findings in three cases of pemphigus.

I don't mean to imply that this should be the main or only diagnostic feature of pemphigus. But, since a clinical diagnosis is not infrequently very difficult, I think one more diagnostic point is important and should be employed when necessary.

DR. I. N. HOLTZMAN: About three or four years ago, Dr. Director at Bellevue Hospital began to section specimens from all our patients with pemphigus, and within a very short time he came to the conclusion that the observation which was described was a correct one. Of course, we have seen fairly consistently at Bellevue Hospital in our cases of pemphigus, intradermal acantholysis with a split right above the basal layer. There are undoubtedly patients

with bullous disease who, clinically, have manifestations of pemphigus and who die and do not show this particular picture, histologically.

We are beginning to question this whole concept of bullous disease. This much we can say: When you find this intraepidermal acantholysis, you can very definitely say that you are dealing with pemphigus. When you do not find it, you cannot say that it is not going to be a fatal disease.

A Case for Diagnosis: Peyroni's Disease. Presented by DR. C. T. CHIARAMONTE.

J. C., a Negro man, aged 58, has noted a mass in the proximal end of the penis during the past three months. There is deviation of penis to the side upon erection. There is palpable a deep nontender, hard, fairly regular mass measuring 2 by 4 cm. in the proximal shaft of the penis. No inguinal adenopathy is present.

A Mazzini test elicited a negative reaction.

Circumscribed Scleroderma (Morphea). Presented by DR. M. M. ESTRIN.
Diagnosis: Dermatomyositis? Lupus Erythematosus? Presented by DR. C. T. CHIARAMONTE.
Lupus Erythematosus, Subacute Disseminated. Presented by DR. M. SILVERMAN.
A Case for Diagnosis: Disseminated Lupus Erythematosus Improved with Cortisone. Presented by DR. M. SILVERMAN.
A Case for Diagnosis: Herpes Zoster Associated with Chronic Lymphatic Leukemia. Presented by DR. C. T. CHIARAMONTE.
Granuloma Annulare. Presented by DR. M. M. ESTRIN.
Hansen's Disease: Leprosy in a Negro Man, Aged 50, Who Spent the First 13 Yr. of His Life in the British West Indies. Presented by DR. C. T. CHIARAMONTE.
Scrofula. Presented by DR. S. H. SILVERS.
Axillary Tuberculous Adenitis. Presented by DR. C. T. CHIARAMONTE.
Psoriatic Erythroderma. Presented by DR. M. SILVERMAN.
Chronic Lichenoid Discoid Exudative Dermatitis (Sulzberger and Garbe). Presented by DR. S. H. SILVERS.
Exfoliative Dermatitis. Presented by DR. M. SILVERMAN.
Case for Diagnosis: Lichen Planus? Drug Eruption? Presented by DR. C. T. CHIARAMONTE.
Steatocystoma Multiplex. Presented by DR. C. T. CHIARAMONTE.
Extensive Vitiligo. Presented by DR. M. M. ESTRIN.

BRONX DERMATOLOGICAL SOCIETY

Charles R. Rein, M.D., *President*

Henry Silver, M.D., *Secretary*

Jan. 18, 1951

Kraurosis Vulvae. Presented by DR. MARTIN V. BOARDMAN.

G. J., a white woman aged 62, a patient at the New York Skin and Cancer Hospital of the New York University-Bellevue Medical Center has had vaginal itching for the past nine years, which time corresponds with the cessation of her menses. At first her complaint was that of "soreness" for which she was given many local applications. Two years ago she received 20 x-ray treatments of unknown dosage. These helped partially, but in the summer of 1950 there was a recurrence of the former complaint, plus itching.

At present there is no alteration in the external genitalia. The labia minora are absent or practically so, the mucous membranes of the entire labia and external vaginal surfaces are gray, are slightly thickened, and show several excoriations.

The histological examination was made by Dr. C. F. Sims. In the upper cutis the collagen had undergone homogenization. In one area and fairly deep in the cutis was a cellular infiltrate of the banal type, with a goodly sprinkling of plasma cells, especially in the center zone. The overlying epidermis was flattened and showed hypergranulosis and hyperkeratosis. The diagnosis was kraurosis vulvae.

Mycologic examination showed no fungi. The serologic reaction of the blood for syphilis was negative.

DISCUSSION

DR. FRANCES PASCHER: This case is interesting aside from the diagnostic problem involved. The erythema on the thighs, around and beyond the atrophic areas, followed the use of a local antipruritic. The contact dermatitis (medicamentosa) appears to be limited to the normal skin, sparing the atrophic areas.

DR. LOUIS CHARGIN: On purely clinical grounds it is not possible to make the diagnosis of kraurosis vulvae. One must get the aid of the histopathologist. The presumptive evidence is that

kraurosis vulvae is present. Far more important is the treatment, which is, at best, a difficult problem, especially with regard to the intractable itching.

DR. RUDOLF L. BAER: Can kraurosis vulvae involve the inner aspects of the thighs, as is the case in this woman? She shows on each thigh, in the area adjoining the inguinal region, a half-palm-sized patch of atrophy and wrinkling.

DR. SAMUEL B. FRANK: A patient under my observation presented typical lichen sclerosus et atrophicus of the perianal area. She gave a history of having had a similar lesion on the vulva which had been pruritic for many years and for which a vulvectomy was performed three months previously. The clinical and pathologic diagnosis was kraurosis vulvae. A review of the slide, however, revealed many features of lichen sclerosus et atrophicus. It is my feeling that the lesion on the vulva which was excised was also lichen sclerosus. While I probably would not have recommended vulvectomy had I seen the patient originally, I must point out that the first relief from itching followed the excision.

DR. HENRY SILVER: Dr. Baer's point is relevant. The atrophic areas on the thigh and perineum suggest lichen sclerosus et atrophicus.

DR. ARTHUR B. HYMAN: The criteria for the diagnosis of kraurosis vulvae are by no means clearly established. Gynecologic as well as dermatologic textbooks give unsatisfactory descriptions of the disease. Cases of true kraurosis, which is an atrophic process, are rare; in most cases there is associated leucoplakia, which is a hypertrophic process. It is within these leucoplakic areas that malignancy supervenes. To ask for positive histologic aid in diagnosis when the definition of the disease as an entity still needs clarification is putting the cart before the horse. Two conditions of the vulva, lichen planus and leucoplakia, can be excluded on histologic grounds, since the microscopic features are usually characteristic. But, the differentiation between kraurosis and lichen sclerosus et atrophicus must be made on clinical, not histologic, grounds. If there are associated typical lesions of the latter disease on other parts of the body, this diagnosis will be accepted for the vulval lesions as well. If such lesions are not found and if it is true that kraurosis is an entity different from, and not a vulval form of, lichen sclerosus et atrophicus, then one might rightly diagnose the condition as kraurosis. Histologically there are certainly insufficient differentiating features between the two conditions.

DR. FRANK E. CROSS: As a precautionary measure one ought to be careful in the use of x-rays in kraurosis vulvae, since it is a precancerous affection. Other remedies, such as administration of antihistaminics or endocrines, should be employed for the relief of itching.

DR. FRANCES PASCHER: Dr. C. F. Sims studied the histologic sections in this case. He was of the opinion that the microscopic findings were undistinguishable from those of lichen sclerosus et atrophicus. The terms lichen sclerosus et atrophicus and kraurosis vulvae have been used interchangeably by many observers, including Hamilton Montgomery (Atlas of Dermal Pathology, Washington, D. C., Registry Press, 1948) and Elisabeth Hunt (Diseases Affecting the Vulva, ed. 3, St. Louis, C. V. Mosby Company, 1948).

DR. LOUIS CHARGIN: If we are to assume that lichen sclerosus and kraurosis vulvae are one and the same disease, then we must accept the assumption that lichen sclerosus can go on to cancer formation, and, so far as I know, lichen sclerosus elsewhere on the body never becomes malignant. Since kraurosis vulvae does lead to cancer, therefore we must conclude that the two diseases are not identical.

DR. MAURICE UMANSKY: Patients suffering from lichen sclerosus of the vulva rarely complain of itching. I think this is a cardinal differential diagnostic point.

Lymphoblastoma. Presented by DR. JOHN GARB.

G. T., a man aged 42, registered at the New York Skin and Cancer Hospital of the New York University-Bellevue Medical Center, presenting lesions on the right forearm of four years' duration. He complains of occasional itching. His general health has been good. He had measles and scarlet fever as a child and asthma with bronchitis until he was 15 yr. old. He has had bilateral inguinal hernias since May 1947.

The first nodule appeared on the right forearm. Within one year similar lesions developed in a discontinuous manner on the arm, mostly upward, reaching considerable size. From January until June, 1949, the patient was treated with 1,500 r of unfiltered x-rays and from May to June with 800 r filtered through 1 mm. Al. The lesions disappeared completely. On

June 22, one week after the last x-ray treatment, there developed at the site of the original growths isolated nodules the size of a match head, which gradually coalesced to form an irregular plaque. Since September, 1949, no new lesions have appeared. The patient has not received any treatment for the new growths.

On the outer surface of the right arm and forearm there is a roughly oval-shaped patch 5 in. (12.5 cm.) in length and 3 in. (7.5 cm.) in its widest diameter. This patch is slightly indurated, purplish, and with a fairly well-defined border. Roughly in the center of its long axis there are a few satellite papules the size of a match head or pea. On diascopic pressure the lesions are easily compressible, revealing a light-purplish stain. In the left axilla there is a tender lymph node the size of a large pea. The lymph nodes in the right axilla, cervical, and inguinal regions are not enlarged. Below the right knee there are depressed scars, the sequelae of healed lesions, which have been present since April, 1949.

The routine laboratory tests, including determination of the sedimentation rate, showed no abnormal findings. The hemogram revealed normocytic anemia and an occasional atypical lymphocyte.

Histological examination by Dr. C. F. Sims showed throughout the entire cutis infiltrated masses composed of round cells and a few cells with vesicular nuclei and coarse chromatin network. These masses were found at all levels in the cutis and also about the sweat apparatus. The overlying epidermis was thinned. There was a patchy pigmentation in the basal-cell layer and a mild hyperkeratosis of a laminated type. Dr. Sims reported that the massive pleomorphic infiltrate favored the diagnosis of lymphoblastoma.

Tests with old tuberculin in concentrations as low as 1 : 1,000 were negative. Roentgenograms of the chest showed no abnormalities.

Microscopic examinations of the sternal marrow showed only a few areas on each slide suitable for study. These smears were quite cellular. An estimated two-thirds of all the nucleated cells were of the myeloid series, which was represented by all forms. The lymphoid series was represented by the usual number of small lymphocytes. In the erythroid series, many normoblasts, including some in the early stage of development, many groups of unaltered platelets, and occasional megakaryocytes, were seen. Red cells showed a central pallor and occasional polychromasia. The slide was not diagnostic.

DISCUSSION

DR. CHARLES WOLF: I believe that we are not dealing with lymphoblastoma of systemic origin, since we have no evidence of visceral involvement. I would therefore consider the case as one of circumscribed lymphoma. These lesions are radiosensitive and respond rapidly to treatment with x-rays, a maximum of 500 r in divided doses.

DR. NORMAN B. KANOF: The clinical picture that this patient presents closely resembles that in a group of cases which Drs. Jessner, Sawicky, and I have been following at the New York Skin and Cancer Unit for the last three years. The lesions are usually discrete, red brown, nodular, somewhat-elevated, smooth, and shiny. In most instances the eruption has appeared on the face, but some have been limited to the extremities, as in this case, and some to the trunk. Differential diagnosis has always involved lupus erythematosus, lymphoblastoma, sarcoid, tertiary syphilis, and drug eruption. Histologically, in these cases rather sharply circumscribed masses of round cells are distributed through the cutis, so far, without evidence of germinal centers. A diagnosis of a leukemic process is understandable, but blood studies of the patients were essentially negative. W. Jadassohn has recently reported such a group under the name of "reticuloses." Perhaps they may be ranged into the lymphocytoma group in the wide sense of the term.

DR. ARTHUR B. HYMAN: Infiltrated, dusky plaques are much commoner on the face than on the extremities in these cases. They have been variously diagnosed, in accordance with the dermatologic fashion and mood of the age. Histologically they show mainly lymphocytic infiltrates, at times with the presence of varying quantities of polymorphonuclear leucocytes, eosinophils, histiocytes, and vascular changes. Some labeled them lymphocytomas; others, Spiegler-Fendt sarcoid. If associated with typical lesions of lupus erythematosus, these plaques may justifiably be considered as deep forms of this disease. Another confusing element is the eosinophilic granuloma which is being reported so extensively in dermatologic literature. The only criterion for this condition is the presence of eosinophils, and on that basis alone this

diagnosis is being only too commonly made. If repeated biopsies are performed and an early lesion shows eosinophils, later ones may not show them, and then a diagnosis of eosinophilic granuloma "sine eosinophils" is made. Without entering into too many complicating suggestions, I might mention that the still-nebulous erythema elevatum diutinum has been offered in the differential diagnosis of these plaques.

DR. HANS H. BIBERSTEIN: In the cases I saw in the early twenties, some of which were published, lesions were generally much smaller than the ones seen nowadays. In addition, the lesions were mainly on the face. However, in the first case which I demonstrated, the lesions were on the arms; they were regular, round, and some almost the size of a penny, brownish, and shiny. The cases which resemble more closely the ones seen nowadays were described by Dr. Stephan Epstein. Some of them responded to arsenic. Good results were obtained with thorium X. They run a benign course. One case observed for a period of 10 yr. was kept under control with arsenic. The blood counts seemed to be normal, but as far as I remember, the lymphocytes usually were in the upper limits of the normal, often between 35 and 50%.

DR. FRANCES PASCHER: I think it would be best to label this an instance of "lymphoblastoma, type undetermined," since the infiltrate is not sufficiently differentiated to warrant any other diagnosis, e. g., Hodgkin's disease or lymphosarcoma. I hesitate to accept the diagnosis of miliary lymphocytoma, since a lymph follicle with a central germinal zone has not been demonstrated. Nor do I agree that this case fits in with the so-called eosinophilic granulomas of the skin. There is no evidence of a granuloma histologically, nor are eosinophils demonstrable in the tissue. At present the condition appears to be limited to the skin. The possibility of visceral or deep lymph node involvement, however, cannot be excluded.

DR. MARTIN V. BOARDMAN: I have an impression that these cases do not have the benign character which the old cases certainly seemed to have. This present case appears to infiltrate and may terminate in a cancerous type.

DR. CHARLES WOLF: I am not surprised at the failure of response in this case because superficial therapy was employed. For a subcutaneous tumor we should have employed x-rays with aluminum filtration; this would have resulted in prompt involution.

DR. JOHN GARB: This lesion may develop into reticulum-cell sarcoma. It is not radiosensitive, because it took 1,500 r of unfiltered x-rays and 400 r filtered through 1 mm. Al. to cause regression of the lesions. The question arises whether one should watch the patient periodically and leave the new and recurred lesions alone or whether one should treat these lesions with intensive radiotherapy. It appears to me that these lesions have a tendency to recur soon after a course of radiotherapy is given, and when they do recur they do so in a more resistant form; while, on the other hand, if left alone, it may be many years before they change and assume cancerous tendencies.

Partial Alopecia of the Eyelashes. Presented by DR. JOHN GARB.

DISCUSSION

DR. JOHN GARB: Alopecia of the eyelids alone is rare. I find only two cases recorded in the literature: one by Sabouraud (Haar bei Alopecia areata, *Dermat. Wchnschr.* **75**:953, 1922, cited in Jadassohn, J.: *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, Vol. 13, Pt. 1, p. 262), 1927, the other published in a Brazilian journal (Marback, H.: Alopecia Areata of the Eyelids, *Arq. brasil. oftal.* **6**:211 [Dec.] 1943).

Pemphigus Vulgaris Under Complete Control for Nine Months with ACTH. Presented by DR. MORRIS LEIDER.
Epithelioma of the Penis, Treated for Granular Inguinale. Presented by DR. JULIUS H. POLLOCK.
Poikiloscleroderma. Presented by DR. ABRAHAM J. ORFUSS.
A Case for Diagnosis (Early Kaposi Sarcoma?). Presented by DR. WILLIAM M. SISKIND.
Perifolliculitis Capitis Abscedens et Suffodiens. Presented by DR. ANDREW G. FRANKS and (by invitation) DR. ERNST M. ROSENBAUM.
Parapsoriasis en Plaques (Brocq). Presented by DR. LOUIS CHARGIN.
Sarcoidosis. Presented by DR. ERNEST W. NATHAN.
Gummata of the Scrotum. Presented by DR. JULIUS H. POLLOCK.
Argyria. Presented by DR. ABRAHAM J. ORFUSS.
Seborrheic Dermatitis: Pustular Psoriasis(?). Presented by DR. MABEL G. SILVERBERG.

METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Henry G. Morgan, M.D., *President*

Harold C. Fishman, M.D., Vice *President*

Stanton B. May, M.D., *Secretary*

Jan. 23, 1951

Varicella. Presented by DR. EDWARD L. MURPHY.

Herpes Zoster. Presented by DR. EDWARD L. MURPHY.

DISCUSSION OF TWO PRECEDING CASES

DR. EDWARD L. MURPHY: The woman arrived from another city on Jan. 6 with herpes zoster of three days' duration. Two weeks later varicella developed in the man, her son-in-law.

Folliculitis (?) Due to Food Allergy. Presented by DR. EDWARD L. MURPHY.

J. T., a 40-yr.-old white man, has a history of grouped follicopustules around the crotch, axillary areas, and dorsum of the right hand for the past 20 yr. This has never cleared up since the original onset. The beard has never been involved, though there have been repeated flare-ups in the other sites.

A test dose of 0.1 cc. of ambo-toxoid® (a toxoid prepared from several strains of staphylococci combined with bacterial antigen) (Squibb) elicited positive reaction in a zone 10 by 14 cm. Iodochlorhydroxyquin (vioform®) cream, ambo-toxoid,® and potassium permanganate have been used in treatment.

DISCUSSION

DR. HAROLD PRICE: We have to consider why this man has had this folliculitis for these many years and try to determine whether there are other factors concerned aside from the infection of the hair follicles. This eruption is in the area of a large number of sweat glands, and the thought occurs to me that there may be some emotional factors concerned here. As long as he continues to sweat, and he has a nice warm moist area there, I don't see how the eruption can ever be cleared up.

DR. EDWARD L. MURPHY: This case was presented not as a diagnostic problem, because I think that folliculitis is all that it amounts to, clinically and histologically; but something came up during the course of treatment that gave us a clue that later proved to be a valuable point.

I treated him with permanganate baths along with the ambo-toxoid® for a long time, and he became pigmented from the permanganate. I suggested that he use lemon juice to clear the pigmentation, which it did; but redness and itching developed on the areas not involved with folliculitis. We then did a patch test with lemon peel, using both the outer and the inner side. The outer side gave a positive reaction. A trial with lemon given internally caused the follicular eruption to become aggravated. An elimination diet was then instituted, and as soon as we got into the citrus group, there was a flare-up. Oranges were all right, but as soon as he ate a half of a grapefruit, he "popped." Nothing else in the diet gave him trouble. However, every time that he had grapefruit he would break out. I'm presenting this case more to show that food sometimes can produce an exacerbation of a folliculitis.

Lupus Erythematosus, Chronic, Profundus. Presented by DR. STANTON B. MAY.

DISCUSSION

DR. HAROLD C. FISHMAN: I think without a biopsy it is impossible to prove the diagnosis of lupus erythematosus.

DR. EDWARD L. MURPHY: I'd like to suggest erythema annulare or granuloma annulare. These lesions struck me as fitting that diagnosis better than lupus erythematosus.

DR. STANTON B. MAY: The lesions will respond to gold therapy rather quickly, and they will relapse quickly. Other characteristics are lack of scarring and lack of epidermal changes in the biopsy. The changes are all in the dermis and are the same as chronic discoid lupus erythematosus there.

DR. FRED F. FELDMAN: For the past four months Dr. Ben A. Newman and I have had the opportunity to observe and study the effects of cortisone in ointment form applied locally to the

lesions of 10 patients with chronic discoid lupus erythematosus and three patients with necrobiosis lipoidica diabeticorum. It occurred to us that topical administration of cortisone might be effective in dermatology after hearing about the successes ophthalmologists were having in ocular inflammatory conditions after topical instillation of this steroid. We are going to publish the results of this study, not because we feel that we have a definitive cure for discoid lupus erythematosus or necrobiosis lipoidica, but because we have observed an improvement of some degree in all our patients with these two treatment-resistant dermatoses who used cortisone topically. Two patients with discoid lupus erythematosus and one patient with necrobiosis lipoidica have a'ready shown almost complete clearing of their eruptions. Cortisone was used in concentrations of 3.3 mg., 5 mg., and 25 mg. per gram of ointment base. We originally used "neobase" (an oil-in-water emulsion base of the washable type), but after one month we substituted polyethylene glycol (carbowax®). We do not know the optimum concentration as yet, but we feel that about 15 mg. of cortisone per gram of base is probably adequate. The tumid type of lupus-erythematosus lesion appeared to respond more rapidly than did the hyperkeratotic type. There have been several reports to indicate that cortisone is effective locally, as borne out by the work of ophthalmologists (Koff, Rome, Woods, and others). Castor and Baker have shown that application of this steroid in alcoholic solution in rats produces thinning of the epidermis, shrinking of sebaceous glands and hair follicles, thinning of collagenous fibers but no change of elastic fibers, and reduction of the number of cellular elements in the cutis. Meyer and Jones have been able to inhibit vascularization of the rabbit's cornea following alkali burns by previously injecting cortisone subconjunctivally. We cannot explain as yet the results we have achieved. We feel that cortisone administered locally may act directly on the collagenous tissue or vascular elements of the dermis. We hope that further study will provide us with more information.

Pityriasis Rubra Pilaris? Vitamin A Deficiency. Presented by DR. WILLARD L. MARMELZAT.
Hyperlipoidemic Xanthoma (Xanthoma Tuberosum). Presented by DR. MAX POPPER.
Triple Symptom Complex (Behçet's Disease)? Periadenitis Mucosae Necroticans Recurrans (Sutton). Presented by DR. STANTON B. MAY.
Dupuytrens Contracture of Hands (Associated Striae on Arms, Chest, and Back)? Presented by DR. JOHN W. WALTERS.
Diagnosis Deferred: Ova? Animal Origin? Anomalous? Presented by DR. ROSE B. SAPERSTEIN.
Fox-Fordyce Disease (?) on One Axilla. Presented by DR. SIDNEY J. ROSE.
Chloasma: Therapeutic Suggestions. Presented by DR. IRVING A. LEWE.
Chloasma? Pigmented Tumor, Due to Contact? Presented by DR. WILLIAM L. MARMELZAT.

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Harold N. Cole Jr., M.D., *Reporter*

Jan. 24, 1951

Psoriasis with Cancerous Nodule Formation on Lower Extremities. Presented by DR. T. A. BALLIEN and DR. R. J. HILFER for DR. H. H. JOHNSON and DR. I. L. SCHONBERG.

DISCUSSION

DR. H. J. PARKHURST: Epitheliomas developed after this patient had had psoriasis for many years, and on examining his hands I found numerous keratoses, which raised the question as to whether or not arsenic might not be a causal factor in the cancerous condition.

DR. G. M. STROUD: As a therapeutic suggestion, I would like to mention my experience with a drug exhibited at the Academy meeting, namely pyromen,® which is a sterile carbohydrate used for intravenous injection. Its action is to stimulate the reticuloendothelial system and increase the secretion of adrenocortical hormones. The dose ranges between 1 and 5 γ for ambulatory use, which is the way I used it for four patients with psoriasis. In three of these, in whom standard treatment was not beneficial, I have noticed definite improvement.

A Case for Diagnosis: Exfoliative Dermatitis. Presented by DR. T. A. BALLIEN and DR. R. J. HILFER for DR. H. H. JOHNSON and I. L. SCHONBERG.

DISCUSSION

DR. BENJAMIN LEVINE: I had a patient with psoriasis which had turned into exfoliative dermatitis. I put an implant of a 50-mg. pellet of testosterone under the skin of the chest wall, and within two weeks the lesions subsided. After three months the psoriasis recurred, and I put another implant in, without results. I then put implants into other patients with psoriasis, without results. Apparently the androgen was of benefit to the exfoliative dermatitis but not to the psoriasis. I have since used it in other cases of exfoliative dermatitis and have also used large doses of estrogens in females, with uniformly good results. This was before the advent of cortisone or corticotrophin (ACTH).

A Case for Diagnosis: (Lichen Ruber Moniliformis? Poikiloderma?). Presented by DR. BENJAMIN LEVINE and (by invitation) DR. N. R. KRUPKIN.

Melanoma on Leg. Presented by DR. I. L. SCHONBERG.

DISCUSSION

DR. G. A. DE OREO: I have gone over some of the records at City Hospital for the past 40 yr. and found that no patient died of metastasis who had not had previous surgical intervention. I checked the cases of over 100 patients. All had had either amputation or wide excision.

DR. G. W. BINKLEY: In regard to treatment, there is a recent note from the Laboratory for Clinical Investigation at the Memorial Center for Cancer and Allied Diseases in New York, wherein Dr. George T. Pack described the experimental use of rabies vaccine for melanomatosis. He had a patient with cancerous melanoma who two years later had three melanotic nodules excised. The following year that patient was given rabies injections after a dog bite. It was not until five and one-half years later that two additional melanotic nodules appeared. This five-and-one-half year period intervening between the appearance of the multiple metastases and the rabies injection was so unusual that, when told about it, Dr. Pack decided to give similar series of rabies vaccine to 12 carefully chosen private patients, with their knowledge. All these patients had generalized melanomatosis. In 10 patients no apparent changes in existing tumors were observed, and they went on to death, the course of their disease apparently uninfluenced. The experiment is still continuing (Pack, G. T.: Note on the Experimental Use of Rabies Vaccine for Melanomatosis, ARCH. DERMAT. & SYPH. **62**:694-695 [Nov.] 1950.)

DR. B. LEVINE: I presented a patient here about three years ago who had a melanoma on the sole of one foot. The consensus was that high amputation should be done. The surgeon instead excised the lesion widely and also did block resection of the lymph nodes and found metastasis. The patient lived about two and one-half years and eventually died with metastasis of the brain.

In another patient who had a melanoma of the eye, the eye was removed—this was about twenty-five years ago—and she is still alive. I removed a melanoma from the buttock of a youngster five years ago, and he is alive, with no evidence of any metastasis.

DR. H. N. COLE: Dr. W. E. Branner had a patient in whom melanoma of the eye was removed. Twenty-five years later this patient had melanotic carcinoma of the liver.

DR. G. H. CURTIS: About two months ago a woman came in who had had an enucleation of the left eye four or five years ago for melanoma. She was sent to the Cleveland Clinic Hospital because of two nodules, one over the sternum and one near the left ear, and they were metastases. She had melanoma of the retina originally.

A Case for Diagnosis (Lichen Planus? Lichen Striatus? Nevus Unius Lateris?). Presented by DR. BENJAMIN LEVINE, DR. I. L. SCHONBERG and DR. N. R. KRUPKIN (by invitation).

Dermatitis Herpetiformis. Presented by DR. MELVIN BRODY, DR. E. L. GLICKSBERG and DR. BENJAMIN LEVINE.

Hypertrichosis Caudalis—Lumbosacralis. Presented by DR. HUGO HECHT.

Psoriasis with Malignant Supervention. Presented by DR. I. L. SCHONBERG.

Scleroderma with Radiographic Evidence of Esophageal Changes Following Cortisone Therapy. Presented by DR. T. A. BALLIEN and DR. R. J. HILFER for DR. H. H. JOHNSON and DR. I. L. SCHONBERG.

A Case for Diagnosis (Lichen Ruber Moniliformis? Poikiloderma?). Presented by DR. BENJAMIN LEVINE and (by invitation) DR. N. R. KRUPKIN.

Acute, Fine, Papular Syphiloderm. Presented by DR. BENJAMIN LEVINE, DR. I. L. SCHONBERG, and (by invitation) DR. N. R. KRUPKIN.

A Case for Diagnosis (Diffuse Idiopathic Atrophy; Parapsoriasis). Presented by DR. T. A. BALLIEN and DR. H. J. HILFER for DR. H. H. JOHNSON and DR. I. L. SCHONBERG.

Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi with Involvement of Lung. Presented by DR. BENJAMIN LEVINE and DR. I. L. SCHONBERG (previously presented at the Meeting of the Central States Dermatological Association, May 6, 1950).

A Case for Diagnosis (Pigmentation). Presented by DR. JOHN R. HASERICK.

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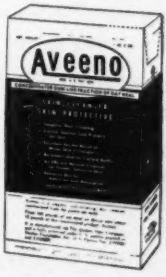

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1 Halpern, Alfred: The Hydrophilic Absorption Ointment Bases, J. Am. Pharm. Assn. XII, pg. 83 (Feb.) 1951.

2 Perrin, Samuel R.: Clinical Safety of Polysorb, Postgraduate Med. 8:485 (Dec.) 1950.

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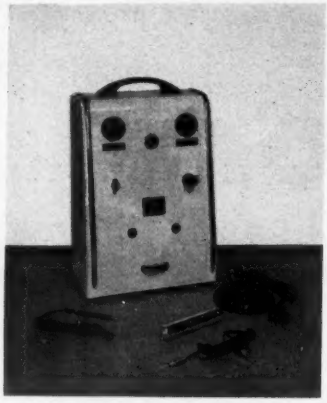

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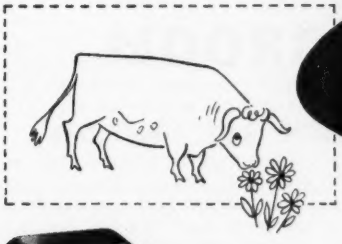

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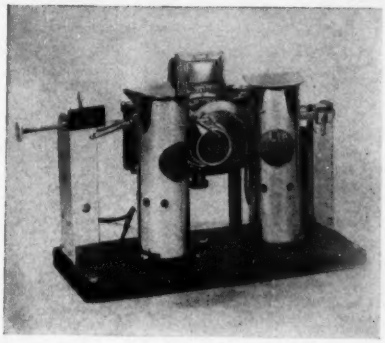

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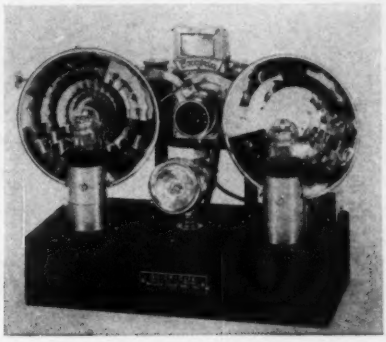

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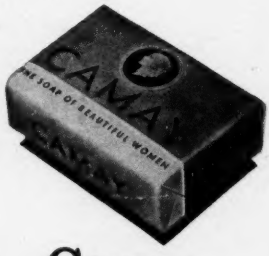

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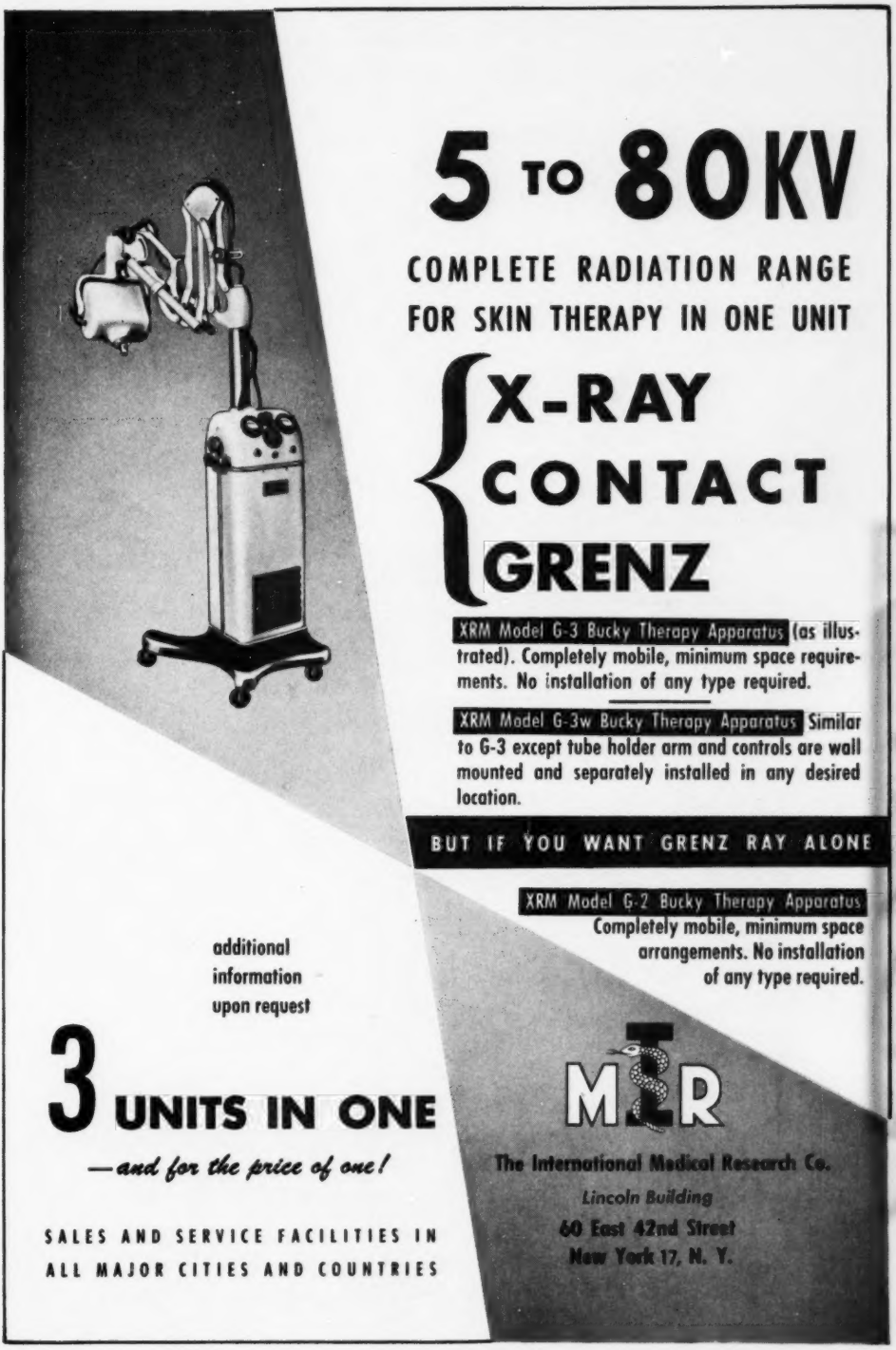

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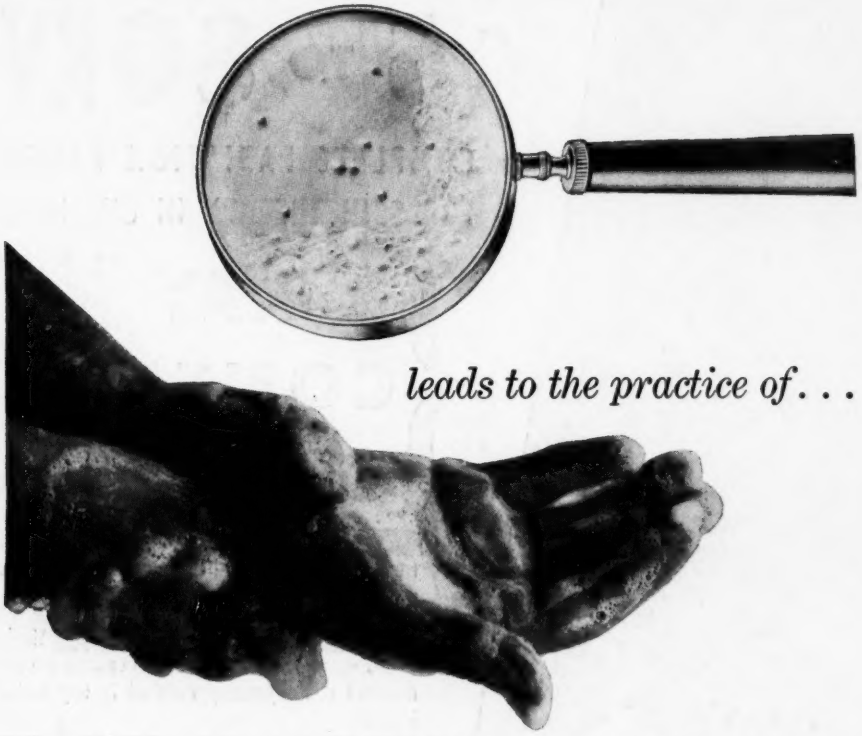
The principle of forbidding soap



leads to the practice of . . .

prescribing pHisoderm – Modern practice includes substitution of pHisoderm, nonalkaline soapless detergent, for soap during the treatment of most dermatoses. Soap impairs the skin's protective "acid mantle," often causes irritation and is keratolytic; it is sometimes allergenic. These factors may aggravate or perpetuate skin lesions.

pHisoderm has a pH value similar to that of the skin (5.5) to assure preservation of its normal physiology. pHisoderm cleans more thoroughly than soap, is emollient, hypoallergenic and more effective in cleansing infectious dermatoses that are due to bacteria and fungi.

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